Electrical Muscle Stimulation in the Intensive Care Setting: A Systematic Review*

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Context: The role of electrical muscle stimulation in intensive care has not previously been systematically reviewed.

Objectives: To identify, evaluate, and synthesize the evidence examining the effectiveness and the safety of electrical muscle stimulation in the intensive care, and the optimal intervention variables.

Data Sources: A systematic review of articles using eight electronic databases (Cumulative Index to Nursing and Allied Health Literature, Cochrane Library, Excerpta Medica Database, Expanded Academic ASAP, MEDLINE, Physiotherapy Evidence Database, PubMed, and Scopus) personal files were searched, and cross-referencing was undertaken.

Eligibility Criteria: Quantitative studies published in English, assessing electrical muscle stimulation in intensive care, were included.

Data Extraction and Data Synthesis: One reviewer extracted data using a standardized form, which were cross-checked by a second reviewer. Quality appraisal was undertaken by two independent reviewers using the Physiotherapy Evidence Database and Newcastle–Ottawa scales, and the National Health and Medical Research Council Hierarchy of Evidence Scale. Preferred Reporting Items for Systematic Reviews guidelines were followed.

Results: Nine studies on six individual patient groups of 136 participants were included. Eight were randomized controlled trials, with four studies reporting on the same cohort of participants. Electrical muscle stimulation appears to preserve muscle mass and strength in long-stay participants and in those with less acuity. No such benefits were observed when commenced prior to 7 days or in patients with high acuity. One adverse event was reported. Optimal training variables and safety of the intervention require further investigation.

Conclusions: Electrical muscle stimulation is a promising intervention; however, there is conflicting evidence for its effectiveness when administered acutely. Outcomes measured are heterogeneous with small sample sizes. (*Crit Care Med* 2013; 41:2406–2418)

Key Words: critical illness; intensive care; neuromuscular stimulation; intensive care–acquired weakness; rehabilitation

***See also p. 2457.**

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IMPLICATION OF KEY FINDINGS:

- Electrical muscle stimulation can be applied early in the ICU admission and overcomes many of the inherent issues associated with active participation required in "traditional" rehabilitation.
- Greater attenuation of muscle mass changes appears to be seen in individuals with less acuity and the chronically critically ill; however, the target population who would benefit most still needs to be determined.
- Optimal stimulation variables and training regimens require further elucidation followed by assessment of efficacy using nonvolitional measures of muscle mass and strength in trials with larger patient populations with long-term follow-up beyond hospital discharge.
- Further research is required to determine the acute and longitudinal safety of electrical muscle stimulation in the critically ill population

Intensive care–acquired weakness (ICUAW) is a common problem following an ICU admission and is associated with prolonged hospitalization (1), delayed weaning (2, 3) and

TABLE 1. Search Strategy

Type of Database	Database	Search Fields	Search Terms
MESH Indexing	CINAHL (all text); EMBASE; MEDLINE; Scopus	Title, abstract, key words	intensive care, critical illness, critical care, or ICU; neuromuscular stimulation, NMES, muscle stimulation, or electric* stimulation*; #1 and #2
Non-MESH Indexing	Cochrane Library; Expanded Academic ASAP; PubMed	Title, abstract, key words	intensive care, critical illness, critical care, ICU; neuromuscular stimulation, NMES, FES, functional electric* stimulation, muscle stimulation, or electric* stimulation; #1 and #2
Non-MESH Indexing	PEDro	Title, abstract, keywords, topic	intensive care muscle stimulation; critical care muscle stimulation; critical illness muscle stimulation

MESH = Medical Subject Heading Indexing, CINAHL = Cumulative Index to Nursing and Allied Health Literature, EMBASE = the Excerpta Medica Database, PEDro = Physiotherapy Evidence Database.

mortality (4, 5). Survivors of ICU have marked functional deficits and prolonged neuromuscular weakness, which can last up to 5 years postdischarge (6), with weakness and fatigue being the most commonly reported physical limitations (7, 8).

Interventions delivered early in critical illness may be the key to minimizing long-term morbidity and protracted impairments in physical functioning. Physical activity has been shown to be both feasible and safe in the ICU setting (9–12), with demonstrable improvements in physical function and strength at hospital discharge (13, 14). However, mobilization relies on the patient being alert and able to engage actively in therapy. Detrimental muscular changes are known to occur rapidly with up to 20% of muscle losses observed in the first week alone (15). As a result, there is growing interest in the use of nonvolitional assistive technologies that facilitate early exercise such as electrical muscle stimulation (EMS) (16, 17), which involves the application of transcutaneous electrodes over the skin, which activate the underlying intramuscular nerve branches to trigger a muscular contraction (18). Although EMS is not a routine part of therapy, it has been shown to have a beneficial effect in preserving muscle mass and strength in healthy immobilized individuals (19–21) and in chronic disease populations (22–24).

Despite the previous publication of narrative reviews and systematic reviews examining the effectiveness of early mobilization (11, 25, 26) and motor physical therapy (including EMS and assisted technologies) in the ICU population (27), this is the first systematic review to investigate the effectiveness of EMS in the ICU setting. The Preferred Reporting Items for Systematic Reviews guidelines have followed to report this review (28).

The objective of this systematic review is to identify, evaluate, and synthesize the literature examining the effectiveness and safety of EMS exercise for individuals in the ICU setting, and optimal intervention variables used.

METHODS

Information Sources

Prior to conducting this review, the Cochrane Library and Physiotherapy Evidence Database (PEDro) were searched to ensure a similar systematic review had not been published. Eight electronic databases Cumulative Index to Nursing and Allied Health Literature (1982–2012), Cochrane Library (2012), Excerpta Medica Database (1980–2012), Expanded Academic ASAP (1994–2012), MEDLINE (1950–2012), PEDro (1999–2012), PubMed (1949–2012), and Scopus (1960–2012) were searched by one reviewer (S.M.P.). A systematic comprehensive and reproducible search strategy was used (**Table 1**) to identify all published studies. Electronic databases were accessed via The University of Melbourne, Australia, and Austin Health, Australia, with the last search run on July 5, 2012.

TABLE 2. Eligibility Criteria

Characteristics	Inclusion	Exclusion
Design	Quantitative study design: RCTs, pseudo-RCTs, cohort studies, case-control studies or case series as per NHMRC classification	Studies not published in a peer-reviewed journal, descriptive commentary, conference abstracts, articles identified as preliminary reports when results are published in a later version
Participants	Adults > 18 years of age in the ICU setting	Animal studies < five participants in the study; weaning or long-stay acute care facilities
Intervention	EMS as an exercise intervention modality applied to peripheral musculature	Diagnostic EMS; EMS for respiratory muscles, i.e., diaphragm
Outcome Measures	Did not form part of inclusion or exclusion criteria	
Publication	No language or publication date restrictions will be applied (on initial search)	

EMS = electrical muscle stimulation, NHMRC = National Health and Medical Research Council, RCT = randomized controlled trials.

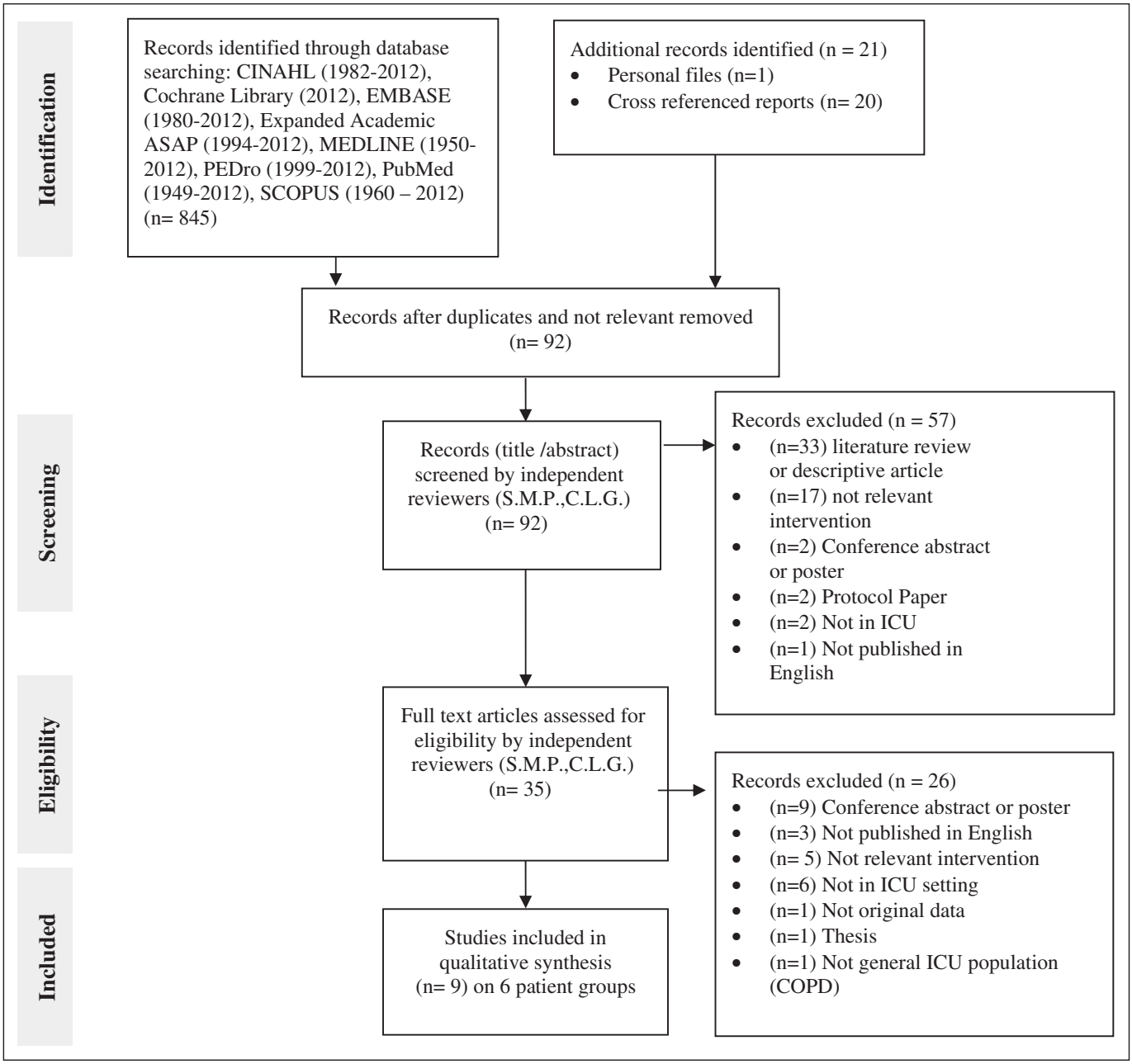

Figure 1. Flow diagram for selection of articles. CINAHL = Cumulative Index to Nursing and Allied Health Literature, EMBASE = the Excerpta Medica Database, PEDro = Physiotherapy Evidence Database.

Additional references were identified by cross-checking reference lists of included articles and searching personal files from authors' own endnote library.

Search

The following search terms were used to search all trial registries and databases: intensive care, critical care, critical illness, neuromuscular stimulation, NMES, muscle stimulation, electric stimulation (Table 1).

Study Selection

The study selection process is outlined in **Figure 1**. Eligibility assessment was performed independently by two reviewers (S.M.P.,C.L.G.) in a standardized manner. All articles identified by the search strategy were assessed based on title and abstract for eligibility against the defined eligibility criteria (**Table 2**). If there was insufficient information to make a decision, full text was sourced and reviewed by two independent reviewers (S.M.P.,C.L.G.) to determine eligibility. Disagreements were resolved by consensus if this was not achieved by a third independent reviewer (L.D.) made the final decision. At each assessment stage, reviewer agreement was estimated with percentage agreement and the Kappa statistics using SPSS for Macintosh statistical software package (Mac SPSS Statistical Version 20, IBM, New York, NY) (29). All references were stored in Endnote software Version X5 (Thomas Reuters, Philadelphia, PA).

TABLE 3. Stimulation Variables–Definition, Measurement, and Application

Stimulation Parameter	Definition	Clinical Application
Amplitude (mA/A)	The amount of energy flowing per unit time	Affects muscle response, i.e., higher intensity = increased excitability (leading to greater muscle torque/force); there is a direct inverse relationship to pulse width, i.e., higher mA required with lower pulse width to elicit muscle contraction
Frequency (Hz)	No. of pulses per second	Affects the quality of muscle contraction and is affected by twitch summation phenomenon—with individual muscle twitches at lower frequencies (~20 Hz), then with increasing frequency level there is overlapping action potential discharge before relaxation is complete leading to summation (30–50 Hz) and stronger muscle contraction; at very high frequencies, the muscle will be in a state of tetany and remain contracted, which means the muscle will fatigue sooner; Can vary frequency depending on training goal, i.e., endurance: low frequency; power: high frequency
Pulse width (μs)	Duration of the stimulation pulse	With greater pulse duration recruit more motor units and thus greater muscle force/torque produced; affected by tissue impedance, i.e., presence of adiposity/edema may mean higher pulse width is required to achieve muscle contraction
Ramp up and ramp down	Current intensity will increase (ramp up) to a preset maximum level and may also decrease (ramp down) in intensity	Ability to alter ramp up and ramp down improves patient tolerance of EMS
On:off time	The length of time the pulse is delivered versus no stimulation	Affects the fatigability of stimulated muscle

A = amplitude, EMS = electrical muscle stimulation, PW = pulse width.

Data Collection Process

A data collection form was specifically developed, and data extracted from the included studies by one reviewer (S.M.P.) and a second reviewer (C.L.G.) cross-checked the data. To avoid double-counting data, multiple reports on the same patient group were identified by juxtaposition of the data from identified studies. All collected data were stored in Microsoft Excel for Mac 2011 (Version 14.2.2, Microsoft Corporation, Redmond, WA).

Data Items

Information was extracted for included studies on: 1) study design—type, first author name and country, publication year; 2) participant characteristics, eligibility criteria; 3) intervention type (muscles stimulated, dosage, stimulation variables (**Table 3** for definition of stimulation variables retrieved), duration, frequency; 4) type of outcome measures and assessment time point(s).

Risk of Bias in Individual Studies

Two independent reviewers (S.M.P.,S.B.) assessed the risk of bias of trials using 1) PEDro Scale designed for randomized controlled trials (RCTs) (30); and 2) Newcastle–Ottawa Scale (NOS) designed for nonrandomized trials (31). Studies were also ranked on the National Health and Medical Research Council Hierarchy of Evidence Scale (32). The scoring criteria used for synthesis of bias risk of included studies were reported as "poor" through "excellent" based on the score calculated in both the PEDro and NOS (33) (**Table 4**).

RESULTS

Study Selection

The search of eight databases (Fig. 1) resulted in 845 studies. Cross-referencing yielded a further 20 potentially relevant studies and one article from personal files. Reports not published in English were excluded ($n = 4$). Authors ($n = 2$) were contacted to determine if studies reported in conference abstracts had been published in a peer-reviewed journal. Both authors responded, and subsequently neither of these studies was included. Two authors were contacted to clarify the setting in which EMS was provided; both reported

TABLE 4. Scoring Criteria Used for Synthesizing Results of Studies in the Review

	PEDro Scale	Newcastle–Ottawa Scale
Excellent	9–10	8–9
Good	6–8	6–7
Fair	4–5	4–5
Poor	<4	<4

PEDro scale = Physiotherapy Evidence Database scale.

TABLE 5. Participant Characteristics in Reviewed Trials

Author, Location	Population	Intervention Group (Electrical Muscle Stimulation)				Control Group			
		n	Age (yr), Median (IQR), or Mean (SD)	Gender Male:Female	Baseline Severity of Illness Scores; Median (IQR)	*n*	Age (yr), Median (IQR)	Gender Male:Female	Baseline Severity of Illness Scores
Bouletreau et al (38), France	8 d ICU hospitalization	10	72 (68–78)	9: 1	NR	Cross-over trial design—same patients in both groups			
Routsi et al (37), Karatzanos et al[a] (35), Gerovasili et al (36, 41), Greece	ICU patients, APACHE II ≥ 13, stratified based on age and gender	24	55 (20)	19:5	APACHE II: 16 (4); SOFA: 8 (3)	28	59 (21)	22:6	APACHE II: 19 (5); SOFA: 8 (3)
Gruther et al (39), Austria	Short- and long-term ICU patients (<7 d and > 14 d, respectively)	16	ST group: 52 (10); LT group: 61 (10)	ST group: 7: 1; LT group: 7: 1	NR	17	ST group: 48 (12); LT group: 64 (8)	ST group: 8:1; LT group: 4:4	NR
Meesen et al (34), Belgium	ICU patients mechanical ventilation > 24 h and prolonged sedation time	7	65.3 (16.5)	3: 4	NR	12	67.2 (13.2)	9:3	NR
Rodriguez et al (40), Argentina	ICU patients with sepsis	14	72 (63–80)	7: 7	APACHE II: 20 (18–27); SOFA: 10 (9–12)	Single legged design, each participant acted as his/her own control			
Poulsen et al (15), Denmark	Septic shock	8	67 (64–72)	8: 0	APACHE II: 25 (20–29); SOFA: 11 (9–14)	Single legged design, each participant acted as his/her own control			

APACHE II = Acute Physiology and Chronic Health Evaluation Two, NR = not reported, SOFA = Sequential Organ Failure Assessment, ST = short term, LT = long term.

[a]Trial from Greece on the same patient cohort with different outcome measures reported across four distinct peer-reviewed journal articles. The participant characteristics are described from the Karatzanos (2012) publication as this was the largest sample size reported on for final analyses for ease of interpretation in this review.

that the intervention was performed in an acute abdominal surgical ward, and the studies were excluded. Almost perfect agreement between the two independent reviewers of potentially relevant titles/abstracts (S.M.P.,C.L.G.) and full-text articles (S.M.P.,C.L.G.) was obtained. Percentage agreement for titles/abstracts was 92%, Kappa = 0.84 and for full text was 100%, Kappa = 1.0 (29). Assessment of title, abstract, and full text resulted in the inclusion of nine articles on six unique participant samples for this systematic review.

Study Characteristics

This review included eight RCTs (15, 34–40) and one case-control study (41). Evaluation of EMS in the ICU is a rapidly growing area of research as evidenced by 40% of the reviewed studies being published within the past year (15, 35, 40). Trials to date have predominantly been conducted in Europe (15, 34–39, 41), and the one remaining trial was conducted in South America (40). The participant characteristics are summarized in **Table 5**. Nine studies involving six valid patient populations in which EMS has been used in a general population of ICU patients totaling 136 participants were included, with two studies specifically including individuals with sepsis (15, 40).

Stimulation variables varied among studies in terms of muscles stimulated, pulse characteristics, amplitude intensity, and exercise session duration (**Table 6**). The quadriceps muscle was stimulated in all studies (15, 34–41). Other muscles stimulated were peroneus longus in one cohort (35–37, 41), gastrocnemius (38), and biceps brachii (40). Pulse width predominantly ranged between 300 and 400 μs, except for one study that used a pulse width of 3,000 μs in combination

with a very low pulse frequency of 1.75 Hz (38). Pulse frequency was more variable compared with pulse width and ranged from 1.75 to 100 Hz across all included studies. The most commonly used frequencies were between 35 and 50 Hz (15, 35–37, 41). One study involved a varying frequency and pulse width during the interventional session (34); however, it was most common for a standard pulse width and frequency to be applied with stimulation intensity (mA) as the main variable modified. Eight trials described the stimulation intensity at a level able to induce a visible contraction (15, 34, 35, 37–39, 41, 42), with one at the patient's maximum tolerable intensity (39). Intervention was commenced either within the first 3 days of ICU admission (15, 35–37, 39–41) or in long-stay ICU cohorts, with time to first intervention session ranging from 8 to 33 days (38, 39). The duration of EMS intervention provided was variable across included studies (Table 3), and the type of muscle training used during intervention (interval training or continuous training EMS) was not specified in any study.

In one study, the control group received sham stimulation (39). In three studies, participants were randomized to unilateral EMS, whereas the contralateral leg of the same participant acted as a paired control (15, 34, 40). Included studies primarily evaluated pretreatment and post-treatment effects. No trials evaluated follow-up beyond intervention cessation.

The main outcome measurements used to examine treatment effect were: 1) muscle thickness and circumference; 2) muscle strength; and 3) biomarker analyses (**Table 7**). The timing and methodology for outcome assessment across trials is described in **Table 8**.

Reporting of adverse events was only specifically stated in three studies (15, 34, 39), with one adverse event reported where a participant sustained a superficial burn due to incorrect stimulation mode setting (40).

Results of Individual Studies

Muscle thickness/volume was evaluated in four studies using ultrasonography or CT (15, 36, 39, 40). EMS administered early (within 3 d of ICU admission) was not shown to attenuate quadriceps (15, 39) or biceps muscle wasting (40) in three studies (**Tables 9** and **10**).

The two studies with higher median Acute Physiology and Chronic Health Evaluation II scores, 20 (40) and 25 (15) at baseline, reported a greater degree of muscle loss and did not demonstrate muscle preservation with EMS (16–20% reduction) compared with the study with a median APACHE II of 16 (36), which demonstrated a greater degree of preservation with EMS (8–14% reduction). Only one study examined muscle thickness in a long-stay ICU participant subgroup with a significant increase in quadriceps muscle thickness in the EMS group (+4.9%) versus sham (−3.2%) (39). Thigh circumference was measured in two studies with conflicting results (34, 40): one study finding a significant attenuation in atrophy (indirectly measured via circumferential measurements) (34) and the other study finding no significant difference between EMS and control groups (40).

Different measures were used to evaluate strength across the four studies that measured this variable, thus limiting the ability to pool the findings. All demonstrated an increase in strength secondary to the application of EMS (37, 40), except for hand-grip dynamometry (which was conducted as a post hoc analysis on a small subgroup) with no significant difference among groups (35). One study examined the clinical diagnosis of ICUAW using the Medical Research Council (MRC) score with a higher prevalence in the control versus EMS group, 11 (39%) versus 3 (12.5%), respectively (37).

Risk of Bias Within Studies

The risk of bias within studies was assessed by two independent reviewers (S.M.P.,S.B.), achieving a percentage agreement of 87%. No studies were excluded from this review based on the assessed bias risk. Consensus was achieved on all occasions. The overall methodological quality of the RCT studies included in this review was rated as "fair" to "good" (33) (Table 4), and six studies achieved a PEDro score between 4 and 8 (Tables 9 and 10). No studies were graded as "excellent," and two studies were graded as "poor" (scoring 2 and 3) (34, 35). Risk of bias in the RCTs was predominantly poorly scored due to lack of blinding (participant and therapist) and lack of intention-to-treat analysis (Table 9). Concealed allocation was only reported in one trial (40), and a high dropout rate was evident across the trials with greater than 15% dropout rate by final analyses in five studies (34–37, 39). The overall quality of the case-control study included was "good" with NOS of 6 (Table 10).

Synthesis of Results

It was not appropriate to conduct meta-analyses or pool results due to the heterogeneous nature of the sample populations, intervention variables, and outcomes measured.

DISCUSSION

Nine studies were identified for inclusion in this systematic review, with four articles published on one patient population in Greece. Therefore, there are only six patient populations in which EMS has been used in a general ICU population.

EMS administered early in the ICU admission period did not demonstrate muscle preservation, particularly in individuals with higher median baseline APACHE II scores (>20) (15, 40). There was greater attenuation of muscle mass changes in individuals who were less severely ill at admission (APACHE II < 16) (36). The timing of intervention delivery was similar regardless of disease acuity. The negative findings of the EMS studies that involved individuals with higher APACHE II scores may be related to critical-illness-induced muscle membrane dysfunction secondary to oxidative stress and sodium channel dysfunction, which may lead muscle tissue to be unexcitable to the effect of EMS (42). Rodriguez et al reported that perceptible muscle contraction was only detected in 77% of sessions, which adds support to this hypothesis (40), and Poulsen et al did not specifically state whether a contraction was observed (15). In comparing the studies above the outcome measures used was different with use of CT volume (15) compared with

TABLE 6. Description of Muscle Stimulation Component of Intervention Programs in Reviewed Studies

	Stimulation Variables and Muscles Stimulated			
References	**Impulse Type**	**Frequency**	**Pulse Width**	**Intensity**
Bouletreau et al (38)	Biphasic symmetric	1.75 Hz	3,000 μs	Induce contraction
Karatzanos et al (35); Routsi et al (37), Gerovasili et al (36, 41) same patient cohort	Biphasic symmetric impulse; on:off time: 12:6 s; ramp time: 0.8	45 Hz	400 μs	Visible contraction
Gruther et al (39)	Biphasic symmetric impulse; on:off time, 8:24 s	50 Hz	350 μs	Max tolerable
Meesen et al (34)	Biphasic symmetric impulse; on:off time—5 min, 90:30 s; 6 min, 10:20 s; 8 min, 10:20 s; 6 min, 7:14s; 5 min, 90:30 s; ramp up, 2 s	5 min: 5 Hz; 6 min: 60 Hz; 8 min: 100 Hz; 6 min: 80 Hz; 5 min: 2 Hz	5 min: 250 μs; 6 min: 330 μs; 8 mins: 250 μs; 6 mins: 300 μs; 5 mins: 250 μs	Visible contraction
Rodriguez et al (40)	Biphasic symmetrical impulse; on:off time, 2: 4 s	100 Hz	300 μs	Visible contraction
Poulsen et al (15)	Biphasic pulses; on:off time, 4:6 s; ramp time, 0.5 s	35 Hz	300 μs	Visible contraction

EMS = electrical muscle stimulation, bd = twice daily, VL = vastus lateralis, VM = vastus medialis A group = acute group, LT group = long-term group, NR = not reported, IQR = interquartile range.

ultrasound (36, 39, 40), this may influence the interpretation of the results. In a further study examining early versus later commencement of EMS (<7 d compared with >14 d; Table 4), muscle mass was preserved in individuals who commenced after 14 days (39). Results from this good-quality article (PEDro = 6) albeit with a small sample of 33 suggest that use of EMS in the chronic critically ill may be beneficial (39). The adequacy of the nutritional status of the participants, an important factor in the maintenance of muscle particularly in the critically ill (43), was reported in only two studies (15, 38).

Two investigators used manual muscle strength testing as an outcome measure (37, 40). There were differences in how the scores were summed to determine differences in strength among groups. Routsi et al (37) assessed mean MRC score of two independent assessors to determine the presence of ICUAW. The median MRC values were 58 versus 52 (out of 60), respectively, for the EMS and control groups, In the trial by Rodriguez et al (40), MRC scores for quadriceps and biceps strength only were evaluated rather than six muscle groups as recommended (3, 44). Although these articles described significant strength increases, given the doubts raised about validity and reliability (45–47) of the MRC sum score and the fact that changes from 52 to 58 represent muscle group strength scores above the ICUAW threshold, there are issues with accepting this result as an indicative of increased strength resulting from the EMS intervention. Furthermore, strength changes from 52 to 58 suggest that the patient may not gain any additional clinical benefit from the intervention, although comparing the relationship of the MRC score with function requires more investigation. Measurement of muscle strength in ICU is an area of current research with authors attempting to identify a more valid measure. Perhaps use of a nonvolitional muscle strength measurement (such as magnetic stimulation of peripheral nerves) (48) would reduce the variability associated with manual muscle testing. If this were feasible, strength testing could potentially be performed earlier in the ICU admission, allowing us to better define the target patient populations to investigate the efficacy of interventions such as EMS.

The included studies encompassed heterogeneous stimulation variables, intervention duration, and intensity. A number of physiological studies have been conducted examining the role of the different stimulation variables—frequency, pulse width, and amplitude on muscle torque production. To increase muscle strength, the force of contraction needs to be increased (muscle torque). The primary means of achieving this is by increasing the intensity (amplitude) or pulse width

Stimulation Variables and Muscles Stimulated				
Muscles Stimulated	**Time Delay Until First EMS Session in Days**	**Session Duration**	**Actual No. of Sessions, Days**	**Time Point at Which EMS Ceased**
Calves, quadriceps bilaterally	8 or 12 (depending on allocation)	30 min bd	4 d	4/7
VL, VM, peroneus longus bilaterally	2	55 min daily	Mean (SD), 8 ± 6 sessions and 82 ± 20% (of session time)	ICU discharge
Quadriceps bilaterally	Mean (SD): A group, 3 (2); LT group, 33 (15)	W1: 30 min; W2–4: 60 min, 5/7, for 4/52	NR	4/52
Rectus femoris, VM right leg	NR	30 min daily	NR	When extubated and off sedation
Biceps and VM unilaterally	Median [IQR]: 2 [1–2]	30 mins bd	13 days [IQR, 7–30]	Until successful extubation (defined by no need for reintubation for ≥ 72 hr or mechanical ventilation ≥ 72 hr in tracheostomized patients
VM, VL unilaterally	NR; Baseline measures assessed: 26 [16–52 hr]	60 min daily	7 d, 100% of treatment duration	Ceased 1/52

of stimulation, which alters the number of motor units/fibers recruited (49, 50). However, at higher frequencies, there is greater potential for fatigue and reduction of muscle recruitability leading to less muscle force (50, 51). Frequencies as high as 100 Hz have been shown to impair and disrupt action potentials and thus muscle membrane excitability (51). In the studies included in this review, frequencies at 35–50 Hz were used. Whether this is the optimal frequency to recruit motor units without causing early fatigue has not yet been investigated. The identification of optimal settings is important because suboptimal muscle stimulation may not achieve effective training outcomes. As with any exercise training, the length of the session and the type of training delivered (interval or continuous training) during the session are important and have not been established. In able-bodied people and athletes, interval training has been shown to be effective (52). The use of EMS and research into its efficacy is still in its infancy. Future elucidation of all of the training variables will improve the clinical application of EMS.

The primary means of detecting muscle contraction in this study was via visible contraction. This is a crude and highly subjective means of detecting contractility with inherent limitations, which can be confounded by factors such as edema. It is essential that objective nonvolitional means of evaluating twitch potentiation and muscle contractility continues to be examined (53) to lead to measurements that can be incorporated into clinical practice at the bedside. This will also enable elucidation of appropriate stimulation variables and assist with determining the safety variables for EMS in this population.

In relation to the safety of EMS it is still difficult to provide definitive evidence because only three of the studies reported on adverse events (15, 34, 39), with only one participant reported to sustain a superficial burn secondary to incorrect stimulation variable setup (40). Further work, including reporting adverse events in articles, is needed to establish safety.

The most appropriate outcome measures or composite set of measures that includes biochemical/cellular, muscle mass/structural changes, and nonvolitional strength assessments and function need to be identified. Currently, ultrasonography is the most promising measurement modality. It is both noninvasive and feasible and has established validity and reliability in intensive care; however, further comparisons with strength and functional outcomes are needed. The studies in this review all examined EMS in a nonfunctional supine position. It may be important to examine the role of functional electrical stimulation that uses electrical stimulation in combination with

TABLE 7. Results From Reviewed Trials on Muscle Thickness, Strength, and Biomarker Analyses

References	Measurement Time Points	Muscle Thickness and Circumference	Muscle Strength	Biomarker Analyses
Bouletreau et al (38)	Baseline and daily for 4 d during intervention period			Urine analyses; significant reduction in excretion of 3MH: EMS (3.15 ± 0.32) vs control (3.78 ± 0.37) μmol/kg/d, $p < 0.01$; creatinine: EMS (72.9 ± 25) vs control (92.4 ± 6.8) μmol/kg/d, $p < 0.01$; nonsignificant difference among groups for nitrogen balance and urea
Routsi et al (37); Gerovasili et al (36, 41); Karatzanos et al (35)	CSD ultrasound: baseline and ~ 1/52 post; muscle strength and HGD: assessed on day of awakening; NIRS: baseline and 45 min postsingle session	CSD (ultrasound) ($n = 26$): CSD decreased in both groups; however, CSD of right RF and VI decreased significantly less in EMS, –8% vs control, –13.9%, $p = 0.029$ and EMS, –12.5% vs control, –21.5%, $p = 0.05$, respectively (36)	HGD ($n = 21$): no significant difference in HGD absolute or relative scores between EMS, 21.4 and control, 14.8 kg; EMS, 60.2% and control, 49.1% (35); MRC scores ($n = 52$): higher MRC score in EMS, 58 (51–60) vs control, 52 (40–58), $p = 0.04$ at awakening (35); significantly higher diagnosis of CIPNM in control, 11 vs EMS, 3 individuals; odds ratio, 0.22 [95% CI, 0.005–0.92], $p = 0.04$ (37)	NIRS ($n = 35$): pre-EMS and post-EMS session nonsignificant change in mean StO_2, 81% vs 83%; oxygen consumption rate during vascular occlusion differed significant pre-EMS and post-EMS, 20% vs 22%, $p < 0.05$; reperfusion rate significant difference pre-EMS and post-EMS, 299%/min vs 375%/min, $p < 0.05$; no difference between StO_2 values pre-EMS and post-EMS in control group (41)
Gruther et al (39)	Baseline and postintervention (4/52)	Quadriceps thickness (ultrasound): significant loss of muscle mass in both the short-term[a] EMS (–36.7%) and sham groups (–38.9%); increase in MLT in EMS (4.9%) vs sham (–3.2%), $p = 0.013$ in long-term group[b]		
Meesen et al (34)	Baseline, every third day until EMS intervention ceased	Thigh circumference: significant reduction in circumference loss in EMS vs control limb, $p < 0.05$.		
Rodriguez 2012 (40)	Circumference, biceps thickness: baseline, every second day until last day of EMS; muscle strength: awakening and last day of EMS	Arm/leg circumference and biceps thickness (ultrasound): no significant differences in circumference or biceps thickness observed between stimulation and control side of body	Biceps and quads strength: muscle strength (MRC) of both biceps and quadriceps statistically significantly higher on stimulation side at awakening and last day of EMS compared with control	

(*Continued*)

TABLE 7. (*Continued*). Results From Reviewed Trials on Muscle Thickness, Strength, and Biomarker Analyses

References	Measurement Time Points	Muscle Thickness and Circumference	Muscle Strength	Biomarker Analyses
Poulsen et al (15)	Baseline and postintervention (7 d)	CT quads volume: quadriceps volume significantly decreased in both stimulation and control legs from baseline to 7 d, EMS, 20%, $p = 0.04$ and control, 16%, $p = 0.03$, with no preservation observed with EMS		

3MH = three-methylhistidine, EMS = electrical muscle stimulation, CSD = cross-sectional diameter, HGD = hand-grip dynamometry, NIRS = near-infrared spectroscopy, RF = rectus femoris, VI = vastus intermedius, MRC = Medical Research Council, CIPNM = critical illness polyneuromyopathy, MLT = muscle length thickness, StO_2 = tissue oxygen extraction, Quads = quadriceps.

[a]Gruther et al (39) defined short-term group as individuals whose arrival to ICU and commencement of EMS therapy was less than 1 wk.

[b]Gruther et al (39) defined long-term group as individuals who had more than 2 wk between ICU admission and commencement of EMS therapy.

TABLE 8. Outcome Measures: Timing and Technique

	Outcome Measures		
References	Muscle Thickness and Circumference	Muscle Strength	Biomarker Analyses
Bouletreau et al (38)			Urine samples: timing—collected daily and preserved with acetic acid, frozen until analysis; procedure/analysis—total nitrogen (micro-Kjeldhal digestion and Nessler procedure), creatinine (Jaffe reaction), and 3MH (gas-phase chromatography); nitrogen balance calculated by adding 2 g to urinary excretion
Routsi et al (37), Gerovasili et al (36, 41), Karatzanos et al (35)	Ultrasonography: timing—day of randomization (second day of admission) and 7 or 8 d after first assessment; ultrasound machine—GE Vivid 7 Model ultrasound scanner with 7.5 MHz linear transducer; Procedure—patient in supine legs flat in extension, probe placed midway between ASIS and midpoint of patella; analysis—CSD of RF and VI	Muscle strength (MMT): timing—day of awakening as determined by ability to follow > 3/5 commands; procedure—MRC-SS (out of 60) assessed by two independent investigators (with no more than 24 hr between measurements); analysis—mean value of MRC score of two investigators used for diagnosis of CIPNM (with cutoff value set at < 48/60); muscle strength (HGD): timing—post-MMT assessment in both hands; procedure—Lafeyette instrument used; patient nearly upright (140 degrees), arm by side elbow at 90 degrees and supported by examiner if needed; angles confirmed by goniometer; grip squeeze over 4–5 s; analysis—single highest score (out of five trials each side) used	Tissue oxygen saturation: timing—pre- and postsingle EMS session or assessed before and then 45 min later (without EMS session in between); procedure—NIRS probe placed on thenar muscle for StO_2 assessment; patient supine; venous and arterial occlusion obtained with pneumatic cuff above elbow and inflated to 50 mm Hg above patient's systolic blood pressure; occlusion retained for 3 min followed by release of ischemia, which lead to reperfusion phase and hyperaemic phase; analysis—StO_2 changes before, during, and after vascular occlusion monitored and recorded; measurement terminated when StO_2 signal returned to baseline value; evaluation of local tissue oxygen consumption rate and microvascular reactivity was then analyzed

(*Continued*)

TABLE 8. (*Continued*). Outcome Measures: Timing and Technique

References	Outcome Measures		
	Muscle Thickness and Circumference	Muscle Strength	Biomarker Analyses
Meesen et al (34)	Circumference: timing—from day of admission every 3 days; procedure—measurement of circumference of both thighs at 5 cm above upper edge of patellar border		
Rodriguez et al (40)	Circumference: timing/procedure—from enrolment to last of EMS, arm, and leg circumferences measured at middle line every 48 h by blinded physiotherapist; ultrasonography: timing—ultrasound machine, 7.5 MHz linear ultrasound transducer; procedure/analysis—biceps thickness measured at middle line (from circumference); limbs passive extension; analysis—CSD of biceps from superficial fat muscle interface to humerus	Muscle strength (MMT): timing—day of awakening as determined by ability to follow 5/5 commands and last day of EMS; procedure—MRC score of biceps and quadriceps force by a blinded physiotherapist	
Poulsen et al (15)	CT scan—muscle volume: timing—baseline and again at 7 d; CT scan—Toshiba Aquilion 64; procedure—muscle volume of quadriceps on CT scan using standardized CT protocol; CT scan (Toshiba Aquilion 64, Tokyo, Japan) of both thighs; measurement—muscle volume of quadriceps; specialized editing program used to process CT images; muscle volume measured between 10 cm proximal and 10 cm distal to the middle of the femur (midpoint between greater trochanter and knee joint line); analysis—% volume change from baseline compared with 7 d		

3MH = three-methylhistidine, CSD = cross-sectional diameter, ASIS = anterior superior iliac spine, RF = rectus femoris, VI = vastus intermedius, MMT = manual muscle testing, MRC-SS = Medical Research Council sum score, MRC = Medical Research Council, CIPNM = critical illness polyneuromyopathy, HGD = hand-grip dynamometry, EMS = electrical muscle stimulation, StO_2 = tissue oxygen saturation, NIRS = near-infrared spectroscopy.

TABLE 9. Risk of Bias in Reviewed Randomized Controlled Trials Using the Physiotherapy Evidence Database Scoring System

References	Criterion						
	Random Allocation	Concealed Allocation	Groups Similar at Baseline	Participant Blinding	Therapist Blinding	Assessor Blinding	Lees Than 15% Dropouts
Bouletreau et al (38)	*	-	-	-	-	-	*
Gerovasili et al (36)	*	-	*	-	-	*	-
Gruther et al (39)	*	-	*	-	-	*	-
Karatzanos et al (35)	*	-	-	-	-	-	-
Meesen et al (34)	-	-	-	-	-	*	-
Rodriguez et al (40)	*	*	*	-	-	*	*
Routsi et al (37)	*	-	*	-	-	-	-
Poulsen et al (15)	*	-	*	-	-	*	*

RCT = randomized controlled trials.

Asterisks indicate criterion fulfilled. Dashes indicate criterion not satisfied.

functional activities such as recumbent cycling, which is currently being investigated in one study in Australia (54).

CONCLUSIONS

Synthesis of findings within this systematic review suggests that EMS is an attractive intervention as it overcomes many of the inherent issues associated with the active participation required in rehabilitation. It may be beneficial in attenuating muscle wasting in the ICU setting, particularly when administered in long-stay ICU participants and those with lower acuity. Further investigation is required in more severely critically ill patients, elucidation of the most effective training regimen, and the safety of EMS.

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Criterion				Design	National Health and Medical Research Council Grade of Evidence
Intention-to-Treat Analysis	Between-Group Difference Reported	Point Estimate and variability reported	Total (0–10)		
-	*	*	4	RCT crossover	II
-	*	*	5	RCT	II
-	*	*	6	RCT	II
-	*	*	3	RCT	II
-	-	*	2	RCT	II
-	*	*	7	RCT	II
*	*	*	5	RCT	II
-	*	*	6	RCT	II

TABLE 10. Risk of Bias in Reviewed Randomized Controlled Trials Using the Newcastle–Ottawa Scale System

Reference	Criterion				Design	National Health and Medical Research Council Grade of Evidence
	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total (0–9)		
Gerovasili et al (41)	*	-	*	6	Case-control	III-2

Data from reference 40.

Asterisks indicate criterion fulfilled. Dashes indicate criterion not satisfied.

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