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Early mobilization for mechanically ventilated patients in the intensive care unit: a systematic review and meta-analysis

Original article

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Abstract: **Background:** Early mobilization (EM) is a regimen that was carried out by physiotherapists in a relatively early stage. It has been investigated by an increasing number of researchers. However, there has not been a meta-analysis concerning whether EM could benefit the clinical outcomes of critically ill patients requiring mechanical ventilation (MV). The present systematic review aims to evaluate the effect of EM compared with immobilization for mechanically ventilated patients.

Methods: A computerized literature search was performed in six databases for related articles from inception to June 2017. We included randomized controlled trials and controlled clinical trials and used the Physiotherapy Evidence Database scale to assess the quality of included studies. Primary outcomes were measures of muscle function, duration of MV, and incidence of mortality. Secondary outcomes were adverse effects and length of stay (LOS) in intensive care unit (ICU) and hospital.

Results: Eight trials were included; of those, only one study without standard EM reported that the intervention was invalid to improve the outcomes. The result of meta-analysis indicated that EM shortened the duration of MV; however, it had no positive effect on mortality and LOS in ICU.

Conclusions: This review suggests that EM improves the muscle function and ventilation duration. Further research highlighting standard intervention and specific groups is needed.

Keywords: *early mobilization • exercise • mechanical ventilation • intensive care unit • meta-analysis • review*

1. Introduction

Mechanical ventilation (MV) is a life-support therapy that improves anoxia, carbon dioxide retention, and acid–base equilibrium. Due to the focus on stabilization of life-threatening pathophysiologic changes, little attention has been paid to neuromuscular and long-term cognitive function in such critically ill patients.[1] Mechanically ventilated patients develop intensive care unit-acquired weakness (ICUAW) as a result of their immobility and sedative administration.[2,3] As the main clinical sign of critical illness neuromyopathy, ICUAW is typically characterized by paresis or limb paralysis, weakened reflection, muscle atrophy, and difficulty in weaning. ICUAW begins within hours of MV, and it was found to be present in 11%–65% of the patients within at least 24 hours.[4,5] It worsens muscle function, increases acute morbidity and 1-year mortality, and prolongs duration of MV and length of stay (LOS) in ICU and hospital.[6–11]

For ICU patients, the term "early mobilization" (EM) refers to the application of physical therapy (for example, passive mobilization, active mobilization, and respiratory muscle training) or novel mobilization techniques (for example, cycle ergometry or neuromuscular electrical stimulation), and EM possesses prominent

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superiority if it is initiated from an early stage (less than 5–7 days).[12,13] As a progressive mobility protocol, the mobilization starts with a series of planned movements and sets the goal of recovering to the previous level of functioning. The protocol consisted of several levels of activities that go forward one by one, and it also stipulates the time, frequency, duration, and suspended condition of intervention.[14] Up to now, EM has been associated with improved muscle function, shorter duration of MV, and decreased LOS in ICU and hospital. Moreover, the study has confirmed that EM is safe and feasible for unstable mechanically ventilated patients.[15]

Clinicians have spotted light on EM since it has been put forward, especially for patients with ventilator. More recently, there has been two systematic reviews about the effects of EM in patients with MV.[16,17] One published in 2013 illustrated the benefits of EM to muscle strength, ventilation duration, and LOS in ICU and hospital.[16] Another that reviewed six studies (three randomized controlled trials (RCTs)) suggested that EM can benefit functional status significantly;[17] however, the time at which mobilization was initiated was not definitely limited in both reviews.[16,17] The prior one included critically ill patients who were not undergoing MV into the review, and the latter one did not process a quantitative synthesis which may provide a powerful evidence.[16,17] This systematic review, strictly defined the initiatory time, was carried out to evaluate the short-term and long-term effectiveness of EM for patients who are mechanically ventilated.

2. Materials and methods

2.1. Search strategy

We searched six electronic databases as follows: PubMed, Embase, ISI Web of Science, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, and Physiotherapy Evidence Database (PEDro). ClinicalTrials.gov was searched, and reference or citation tracking was identified. The search strategy used a combination of controlled vocabulary and free text terms. We restricted the search to articles published in English language from inception to June 2017.

2.2. Study selection

Original research reports from RCTs or controlled clinical trials (CCTs) were included if they meet each of the following criteria: (1) population: subjects were adults (aged ≥18 years) who had been on MV for no more than 5 days and followed up until hospital discharge; (2) intervention: EM therapy included physical therapy, occupational therapy, respiratory muscle training, and novel mobilization techniques using cycle ergometry or neuromuscular electrical stimulation; (3) comparison intervention: usual care without EM during MV period, self-control studies were also included; (4) outcome measures: primary outcome measures were measures of muscle function (for example, muscle strength and muscle volume), duration of MV, and rate of mortality. Secondary outcomes were ICU LOS, hospital LOS, and adverse effects.

2.3. Data extraction

Titles and abstracts were independently screened by two reviewers; studies that seemed to be potentially relevant were full-text screened according to the inclusion criteria. Data were extracted independently by one reviewer and checked by another reviewer, and a predesigned data extraction form was used. The form included the setting, time frame, baseline characteristics of participants, intervention, and outcomes of every studies.

2.4. Quality assessment

Studies were assessed by two independent reviewers using the PEDro scale,[18] which is an 11-item checklist developed to assess the methodological quality of physiotherapy intervention. The summary score of ≥5 or ≥6 points of a study was defined as adequate quality. The PEDro scale also evaluates the risk of bias. Any inconsistency among reviewers was resolved by discussions.

2.5. Statistical analysis

Meta-analysis was performed with Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). We calculated the mean difference (MD and 95% CI) for continuous variables, and if the units of measurements were different, we used standard MD (SMD). For dichotomous outcomes, we merged data by using risk ratios (RRs) and 95% CIs. The statistical consistency was measured by I^2. An inverse variance method with the fixed-effect model was used if low statistical inconsistency was detected ($I^2 \leq 25\%$), and when moderate or high statistical heterogeneity was found the random effects model was used ($I^2 > 25\%$). When the number of included studies was small in a heterogeneity set, a fixed-effect model was adopted.[19]

Statistical significance was set at 0.05 for hypothesis testing and at 0.10 for heterogeneity testing. Sensitivity analyses were conducted for the outcomes excluding trials with high risk of bias, distinctive patients, or intervention.

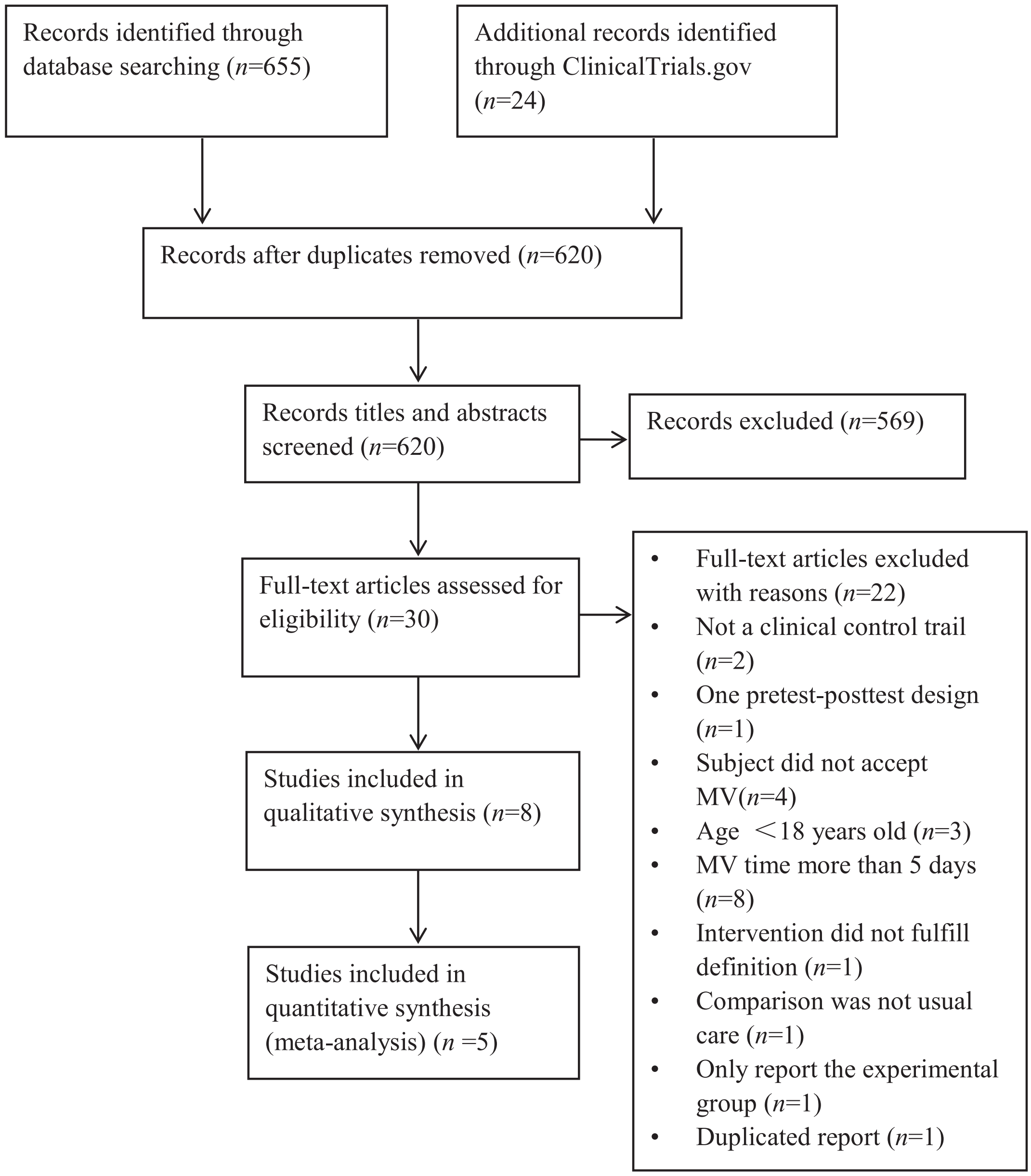

Figure 1. Flow diagram of process for identification of included studies.

3. Results

3.1. Study selection

In this systematic review, the search in all databases yielded 655 potentially relevant articles. Of those, seven registered clinical trials have been completed, but there were no study results posted. After screening the titles and/or abstract, 30 full-text articles were selected (Figure 1). Twenty-two studies failed to meet the inclusion criteria, and thus, eight studies (seven RCTs and one CCT) were included in the qualitative synthesis[20–27] and five[20–24] included in the meta-analysis. The main characteristics about the study design, population, intervention of the experimental and control groups, and outcome measurement of the studies are shown in Table 1.

3.2. Methodological quality

The PEDro score of individual studies ranged from 5 to 7 with a mean score of 6 (Table 2). Seven studies used a randomized method for allocation,[20,22–27] and one study was based on block allocation.[21] Two studies mentioned the concealment of the allocation.[22,27] Blinding of the

Study	Design	Participants	Intervention	Outcomes
Dong et al. 2014[20]	RCT	Exp: *n*=30 (male 70.0%); Age (y) =55.3 (16.1); APACHE II=15.0 (4.2) Con: *n*=30 (male 66%); Age (y)=55.5 (16.2); APACHE II=16.0 (4.1)	Exp: EM Con: no mobility	Duration of MV Mortality ICULOS
Morris et al. 2008[21]	CCT	Exp: *n*=145 (male 56.4%); Age (y) =54.0 (16.8); APACHE II=23.5 (8.8) Con: *n*=135 (male 53.3%); Age (y) =55.4 (16.8); APACHE II=23.5 (8.8)	Exp: EM Con: no mobility	Mortality Duration of MV ICULOS Hospital LOS
Schweickert et al. 2009[22]	RCT	Exp: *n*=49 (male 41.0%); Age (y) =57.7 (36.3-69.1)*; APACHE II=20 (15.8-24)* Con: *n*=55 (male 58.0%); Age (y) =54.4 (46.5-66.4)*; APACHE II=19 (13.3-23)*	Exp: EM Con: ordered by the primary care team	Duration of MV ICULOS
Patman et al. 2001[23]	RCT	Exp: *n*=101 (male 80.0 %); Age (y) =62.8 (12.2) Con: *n*=102 (male 71.0 %); Age (y) =63.3 (14.4)	Exp: EM Con: physiotherapy	Duration of MV ICULOS Hospital LOS
Caruso et al. 2005[24]	RCT	Exp: *n*=12 (male 67.0%); Age (y) =67 (10); APACHE II=23 (6) Con: *n*=13 (male 69.0%); Age (y) =66 (17); APACHE II=24 (7)	Exp: EM Con: no inspiratory muscle training	Duration of MV
Meesen et al. 2010[25]	RCT	Exp: *n*=7 (male 42.9%); Age (y) =63.5 (16.5) Con: *n*=12 (male 75.0%); Age (y) =67.2 (13.2)	Exp: stimulated by an electro-stimulator Con: no stimulation	Thigh circumference Cardio-respiratory characteristics
Poulsen et al. 2011[26]	RCT	Exp: *n*=8 (male 100%); Age (y) =67 (64–72); APACHE II=25 (20-29) Con: patients served as own control	Exp: stimulated by a battery-stimulator Con: no stimulation	Quadriceps muscle volume
Rodriguez et al. 2012[27]	RCT	Exp: *n*=14 (male 50%); Age (y) =72 (63-80); APACHE II= 20 (18-27) Con: patients served as own control	Con: patients served as own control Con: no stimulation	Quadriceps muscle strength Limb circumference Biceps thickness

Table 1. Characteristics of included studies.
Note: Data are presented as number (%) or mean ±SD; *median (interquartile range).
Abbreviations: Exp, experimental group; Con, control group; APCHE II, Acute physiology and chronic health evaluation II score; MIP, maximal inspiratory pressure; BMI, body mass index; FiO2, fraction of inspiration O2; PaO2/FiO2, oxygenation index.

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	<15% dropouts	Intention to-treat analysis	Between-group difference reported	Point and variability reported
Dong et al. 2014[20]	Y	N	Y	N	N	N	Y	N	Y	Y
Morris et al. 2008[21]	N	N	Y	N	N	N	Y	Y	Y	Y
Schweickert et al. 2009[22]	Y	Y	Y	N	N	Y	N	Y	Y	Y
Patman et al. 2001[23]	Y	N	Y	N	N	N	N	Y	Y	Y
Caruso et al. 2005[24]	Y	N	Y	N	Y	N	Y	N	Y	Y
Meesen et al. 2010[25]	Y	N	Y	N	N	N	Y	N	Y	Y
Poulsen et al. 2011[26]	Y	N	Y	N	N	N	Y	N	Y	Y
Rodriguez et al. 2012[27]	Y	Y	Y	N	N	N	Y	N	Y	Y

Table 2. PEDro scores for included studies.

therapist was carried out only in one study.[23] Two studies fulfilled the blinding of the assessors.[22,27] Two studies included had an inadequate follow-up.[22,23] Intention-to-treat analysis was achieved in three studies.[21–23] All studies have described groups similar at baseline and reported the between-group difference and point estimate and variability. Two studies were considered as high methodological quality for the reason that they achieved the random allocation, concealed allocation, and blind outcome assessor.[22,27]

3.3. Participants

Of the eight studies, 713 patients participated in the systematic review. Of whom, 344 (48%) patients were included in the experimental group and 347 (49%) in the control group, and 22 (3%) patients served as own control. Males accounted for 63%. Patients were admitted with ARDS, acute lung injury, acute respiratory failure (38%), cardiovascular and neurological diseases (10%), and post-operation (38%). These studies were carried out in the United States,[21,22] China,[20] Brazil,[24] Belgium,[25] Australia,[23] Denmark,[26] and Argentina.[27]

3.4. Intervention

The detailed description of the intervention for experimental and control groups is reported in Table 1.

All studies started the intervention within 72 hours after subjects were mechanically ventilated. Of those, two studies could be labeled as advanced, since in one study[23] intervention started following the surgery and in another study[25] it started from the first day after admission. In the study by Schweickert et al.,[22] the control group could be categorized as delayed start since the therapy was initiated at 7.4 days.

The frequency of EM is once daily,[22] twice daily,[20,24,27] or three times daily. One study did not provide detailed information on the frequency of intervention.[23] Concerning the duration of sessions, one study reported 20 minutes,[21] two studies were limited to 30 minutes,[24,25] and two limited to 60 minutes.[24,25] Three studies related to electrical stimulation (NMES) all used stimulation for thigh muscle,[25–27] two for quadriceps muscle specifically, and their pulse width of the stimulation was 300 μs.[26,27] In addition, the stimulation intensity increases until a visible muscle contraction is observed.[25,27]

The duration of mobilization has been reported in seven studies.[20–23,25–27] The experimental groups received therapy intervention during the MV phase in four studies,[23,25–27] and one study lasted 7 days.[26] In the studies by Dong et al.[20] and Schweickert et al.,[22] intervention continued until patients returned to a previous level of function or discharged. Only one study[21] ended the intervention when the patients were transferred to a regular bed.

3.5. Effects of intervention

3.5.1. Muscle function

There were three reports of studies representing outcomes of muscle function by measuring the muscle circumferences, muscle strength, and muscle volume.[25–27] The reviewers failed to pool data of the studies to confirm the effect of NMES on muscle function, which attributes to the notable heterogeneity of outcome measurement.[25–27] Meesen et al.[25] reported a marginally significant increase in the circumference of the thigh for the NMES group, similarly, Rodriguez et al.[27] reported a significant increase in arm circumference of the NMES side, and this study also demonstrated that muscle strength of biceps and quadriceps was associated with ES intervention, especially to the patients who had higher APACHE II scores. Meesen et al.[25] also summarized that NMES had a significant positive effect on the prevention of muscle atrophy, whereas in the study of Poulsen et al.,[26] there was no difference in muscle volume between the stimulated and the nonstimulated side for the same patients with septic shock.

3.5.2. Duration of MV

Five studies with 679 participants specifically provided pooling data to demonstrate the effect of EM on the ventilation duration;[20–24] therefore, a fixed-effect model was used. As the unit of measurement was different, we calculated SMD as the result. The overall effect was significant (SMD = 0.16 hours, P = 0.04) with moderate heterogeneity (I^2 = 52%) (Figure 2). Four studies reported that the intervention had an effect on shortening the duration;[20–22,24] however, Patman et al.[23] reported that nonstandard EM during the postoperative intubation period did not improve the duration. The effect of standard EM is robust in a sensitivity analysis restricted to nonstandard (Figure 3).

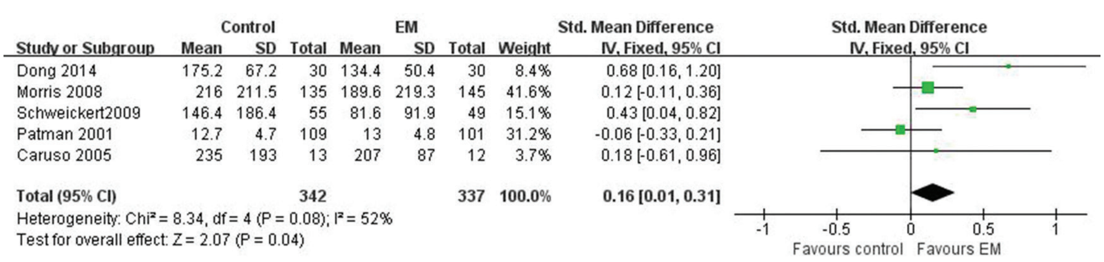

Figure 2. Forest plot for the effect of EM on duration of MV.
Abbreviations: EM, early mobilization; MV, mechanical ventilation.

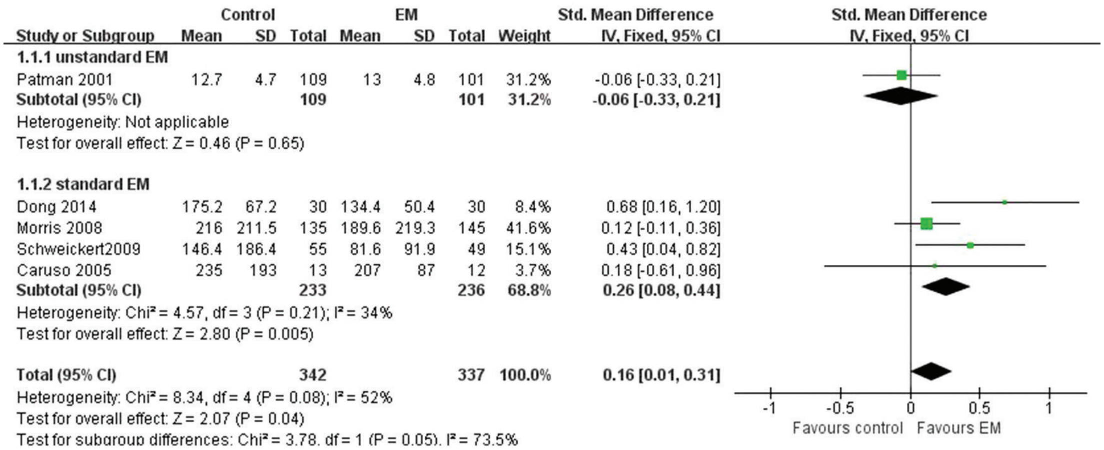

Figure 3. Subgroup analysis of the effect of EM on duration of MV according to standard intervention.
Abbreviations: EM, early mobilization; MV, mechanical ventilation.

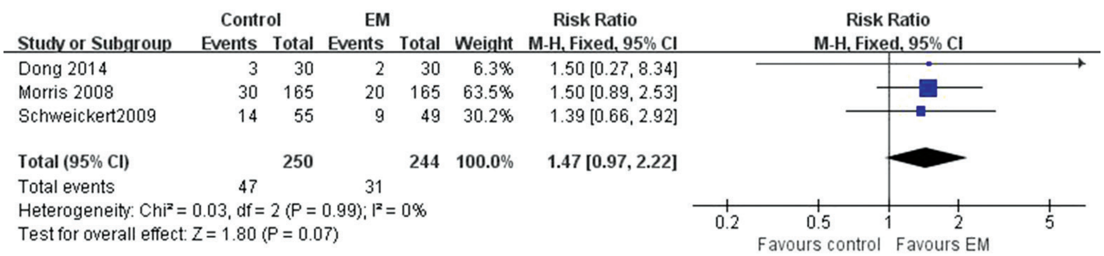

Figure 4. Forest plot for the effect of EM on mortality rate.
Abbreviation: EM, early mobilization.

3.5.3. Incidence of mortality

Mortality rate was reported out of three studies and 494 participants reported incidence of mortality as an outcome measure.[20–22] The overall effect shows that EM was unable to significantly decrease the risk of mortality (pooled RR: 1.47; CI: 0.97–2.22) but favored the EM groups (Figure 4).

3.5.4. LOS in ICU and hospital

Four studies, involving 654 participants, provided data for pooling with a fixed-effect model to show the effect of EM on ICU LOS; the result showed no significant difference,[20–23] and a high heterogeneity appeared ($I^2 = 71\%$) (Figure 5). Results of 3 studies showed a significant shortening in days favoring EM over control, but Patman et al.[23] reported that EM did not reduce the stay, which might also be due to the nonstandard movement according to the sensitivity analysis. Two studies reported the hospital LOS.[21,23] Morris et al.[21] found a significant difference in hospital LOS between experimental and control groups ($P = 0.006$), whereas Patman et al.[23] reported no significant difference between groups ($P = 0.25$).

3.5.5. Adverse effects

Three studies reported information regarding adverse effects in experimental groups;[20,22,25] serious adverse events were rarely reported. Only Schweickert et al.[22] reported an inadvertent removal of radial arterial catheter and decreased oxyhemoglobin saturation. Meesen et al.[25] reported the absence of significant modulation in cardiorespiratory characteristics during or after NMES when compared with their baseline levels. Altogether, EM intervention was considered safely.

4. Discussion

To the best of our knowledge, passive and active mobilizations can prevent muscle atrophy as it preserves the architecture of muscle fibers. Early inspiratory muscle training increases the strength and endurance of accessory inspiration muscles and diaphragm, by increasing

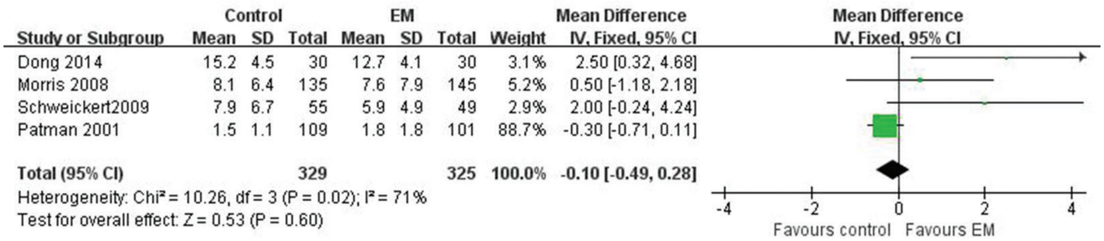

Figure 5. Forest plot for the effect of EM on length of stay in ICU.
Abbreviations: EM, early mobilization; ICU, intensive care unit.

the ventilator-free days to the extent that it could lessen LOS in ICU and hospital. NMES also appears to prevent muscle atrophy, and its improving effects on dyspnea have been supported by Pan et al.[28] Although the effect of EM remains controversial, to explore and deliberate the role of EM undergoing with MV is worthwhile.

This systematic review showed that the evidence whether EM could benefit the functional state is not comprehensive. Studies have indicated that EM could significantly increase the muscle circumference and muscle strength,[25,27] which is consistent with previous trials conducted in non-ICU patients with COPD or chronic heart failure.[29–32] However, muscle volume was unaffected in septic shock patients,[26] the reasons may be associated with the severity of illness and the inflammatory response.[33] The result of meta-analysis shows that in comparison with usual care there is statistical significance for EM to benefit the duration of MV. From the result of subgroup analysis, we concluded that the heterogeneity derive from one included study, unlike the other four studies that did not enact and carry out standard intervention,[23] standard EM protocol that incorporates detailed intervening measurement, initiatory or suspended criterion, intervening duration was not reported, and the intervening process was undemanding. The result has shown no advantage in using EM to decrease the incidence of mortality, which is largely influenced by patients' state of an illness. The intervention may be invalid to shorten LOS in ICU and hospital; in the same way, the result may be interrupted by Patman's study.[23] We realized that patients following cardiac surgery suffer less time in ICU, so EM intervention was not enough to improve stay time within a relatively short time. Meanwhile, studies have reported the favorable influence on the first day out of bed,[20] independent functional status, and greatest walking distance before hospital discharge.[22] Altogether, considering the small number of included studies and clinical diversity, evidence to support the positive effect of mobilization in mechanically ventilated patients at early phase is currently insufficient, and further relevant study is needed.

Despite the quality of the included studies was acceptable, there were still several deficiencies that may cause biases. Since only three studies specified the precise method of randomization, and two studies have not measured the primary outcomes in more than 85% of the participants while there were no countermeasures to deal with the high rate of dropouts, the selection biases might be caused. Although blinding patients or therapists is pragmatically challenging in this type of interventional trial, assessor blinding is feasible but it appeared just in few studies, as a result the measurement bias might be induced. The review of 713 participants has carried out an extensive literature research; nevertheless, given that the conference literature and unpublished literature were not retrieved and non-English language publications were excluded, publication bias may occur. Besides, our review has some limitations as follows: for included patients the diagnosis on admission were diverse; the sample sizes and EM protocols were different from each other; the clinical diversity affects the pooled result apparently; there was minority report about muscle function, which is a direct element that influences other outcomes (for example, duration of MV, LOS in ICU, and hospital); and long-term follow-up after hospital discharge was unavailable.

Growing number of studies reporting EM therapy for patients who are receiving MV indicate obvious benefits, whereas the clinical application is still restricted.[34–37] The current state of application may be associated with a couple of main reasons. First, the acknowledged barrier to mobilize patients with MV was deep sedation, to a large extent early ICU sedation practice affects clinical outcomes,[38] so daily interruption or absence of sedatives predicts an increased probability of ambulation. Another barrier is that the patients' exercise tolerance for cardiovascular stability of critically ill cannot be neglected. Although physiologic stability displayed no deterioration during or after mobilization,[39] for the purpose of safety and effectivity, a standard program including an interprofessional team is required.[40] Currently, a reproducible treatment strategy—the ICU EM quality improvement project—has been expanded and implemented across the three institutions where the plan-do-study-act model was applied;[41] the project will encourage widespread adoption of EM. The third one is staffing, considering that the majority of nurses and physical therapists thought that EM therapy increased work stress and prolonged work time,[42] an interprofessional team composed of physician, full-time physical therapist, full-time occupational therapist, and ICU nurse practitioner is imperative.[1] In this team, the physician makes medical decision, the physician and occupational therapist evaluate patients' state and lead the implementation, and the nurses assist and discuss with them.[23,43,44]

Since our review only included seven RCTs, large-scale RCTs are required to supplement our findings and investigate the effects of EM in mechanically ventilated patients. Attribute to the patients' condition, critically ill patients who required MV are frequently seriously ill or insensible, nonetheless some mobilization requires patients' cooperation. In addition, it is actually tough to establish a true and ethical control group excluding confounding factor to confirm the effect of EM.[11] Therefore, further first-class evidence should regard the standard protocol and rigorous control, and the issue whether EM application is useful to prevent ICU delirium also needs more exploration.

5. Conclusions

This review suggests that EM improves the muscle function and ventilation duration. Further research highlighting standard intervention and specific groups is needed.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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