Dose of Early Therapeutic Mobility: Does Frequency or Intensity Matter?

Biological Research for Nursing
2018, Vol. 20(5) 522-530
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1099800418780492
journals.sagepub.com/home/brn

Chris Winkelman, RN, PhD, CCRN, ACNP, FCCM¹ ,
Abdus Sattar, PhD², Hasina Momotaz, MS², Kimberly D. Johnson, RN, PhD³,
Peter Morris, MD⁴, James R. Rowbottom, MD, FCCP⁵, John Daryl Thornton, MD, MPH⁶,
Sheryl Feeney, BSN, RN-BC⁷, and Alan Levine, PhD⁸

Abstract

Objective: Investigate the feasibility of a nurse-led mobility protocol and compare the effects of once- versus twice-daily episodes of early therapeutic mobility (ETM) and low- versus moderate-intensity ETM on serum biomarkers of inflammation and selected outcomes in critically ill adults. **Design:** Randomized interventional study with repeated measures and blinded assessment of outcomes. **Setting:** Four adult intensive care units (ICUs) in two academic medical centers. **Subjects:** Fifty-four patients with > 48 hr of mechanical ventilation (MV). **Intervention:** Patients were assigned to once- or twice-daily ETM via sealed envelope randomization at enrollment. Intensity of (in-bed vs. out-of-bed) ETM was administered according to protocolized patient assessment. **Measurements:** Interleukins 6, 10, 8, 15, and tumor necrosis factor- α were collected from serum before and after ETM; change scores were used in the analyses. Manual muscle and handgrip strength, delirium onset, duration of MV, and ICU length of stay (LOS) were evaluated as patient outcomes. **Main Results:** Hypotheses regarding the inflammatory biomarkers were not supported based on confidence intervals. Twice-daily intervention was associated with reduced ICU LOS. Moderate-intensity (out-of-bed) ETM was associated with greater manual muscle test scores and handgrip strength and reduced occurrence of delirium. **Conclusion:** Findings from this study suggest that nurses can provide twice-daily mobility interventions that include sitting on the edge of the bed once patients have a stable status without altering a pro-inflammatory serum biomarker profile.

Keywords

ICU, mobility, delirium, muscle strength, mechanical ventilation, rehabilitation, cytokines

Over 1 million adults hospitalized annually in United States. Intensive care units (ICUs) experience long-term dysfunction from ICU-acquired weakness and cognitive impairment (Kress & Hall, 2014; Pandharipande et al., 2013). Early therapeutic mobility (ETM) is recommended to improve the health status of ICU survivors (Barr et al., 2013; Girard et al., 2017; Nydahl et al., 2017). Understanding patient responses to ETM is critical for bedside clinician decisions around implementing this therapy.

Inflammation is common in many illnesses seen in the ICU (Cerejeira, Firmino, Vaz-Serra, & Mukaetova-Ladinska, 2010; Grandt et al., 2010; Truong, Fan, Brower, & Needham, 2009). Abnormal levels of inflammatory biomarkers are associated with loss of muscle mass and strength and delirium onset (Fan, 2012; Kayambu, Boots, & Paratz, 2015; Witteveen et al., 2017). Regular activity, even at a low intensity, might reduce the pro-inflammatory profile of acute and chronic disease (Astrom, Feigh, & Pedersen, 2010; Goldhammer et al., 2005; Pedersen, 2011a). Determining whether ETM influences inflammatory cytokines may help guide clinical decisions about the “dose” intensity and frequency of the intervention in the ICU.

¹ Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, OH, USA

² Department of Epidemiology and Biostatistics, School of Medicine, Case Western Reserve University, Cleveland, OH, USA

³ College of Nursing, University of Cincinnati, Cincinnati, OH, USA

⁴ Division of Pulmonary, Critical Care and Sleep Medicine, University of Kentucky HealthCare System, Lexington, KY, USA

⁵ Department of Anesthesiology and Perioperative Medicine, University Hospitals, Cleveland Medical Center, School of Medicine, Case Western Reserve University, Cleveland, OH, USA

⁶ Pulmonary and Critical Care, MetroHealth Medical Center, Cleveland, OH, USA

⁷ The MetroHealth System, Cleveland, OH, USA

⁸ Department of Pharmacology, School of Medicine, Case Western Reserve University, Cleveland, OH, USA

Corresponding Author:

Chris Winkelman, RN, PhD, CCRN, ACNP, FCCM, Frances Payne Bolton School of Nursing, Case Western Reserve University, 10900 Euclid Ave., Cleveland, OH 44106, USA.

Email: chris.winkelman@case.edu

In the present study, our primary purpose was to examine whether the delivered intervention influenced inflammatory serum markers. We hypothesized that twice-daily and moderately intense levels of ETM would alter systemic inflammatory serum biomarkers, reducing the hyperinflammatory profile common to critical illness and that this alteration would be greater than that seen in participants receiving either a once-daily or a low-intensity intervention. A secondary purpose was to explore whether the dose of the delivered intervention influenced patient outcomes. We hypothesized that twice-daily and moderately intense levels of ETM would improve systemic markers of health and function (i.e., duration of mechanical ventilation [MV], ICU length of stay [LOS], muscle strength, and delirium) to a greater extent than interventions that were maximized at once daily or low intensity.

We chose to measure selected pro- and anti-inflammatory serum biomarkers—interleukins (IL)-6, IL-8, IL-10, IL-15, and tumor necrosis factor- α (TNF- α)—based on their relationship to muscle health (Pedersen, 2011a, 2011b; Winkelman, 2013). Online Supplemental Table S1 describes the biomarkers and rationale for selection for this project.

Materials and Method

This feasibility, interventional study had a repeated-measures design. Patients were randomized to receive ETM at a frequency of either once or twice daily. ETM intensity was based on clinical evaluation in consultation with the team providing direct care to the patient, adhering to an established protocol (Morris et al., 2008). We categorized intensity as “low” (i.e., delivered as in-bed range of motion [no resistance] or passive transfer to a chair that provided full support; there was no or very limited volitional muscle activation) or “moderate” (i.e., sitting at edge of bed, standing, pivot transfer to bedside chair, marching in place at bedside, or walking). For purposes of analysis, we coded ETM activities as the highest intensity for each day.

For the analysis of serum biomarkers, we used the difference between the resting value and the value obtained immediately after the ETM intervention (change score). The rationale for using the change score was to evaluate variation over time congruent with the research questions. The literature suggests that cytokines are altered in 20–30 min in the presence of mild-to-moderate activity, so we collected serum 20 min after cessation of the intervention (Pedersen, 2000, 2011b). C-reactive protein (CRP) changes with highly intense activity sustained over 30 min, so we collected only baseline CRP to establish an inflammatory baseline profile (Fischer, Berntsen, Perstrup, Eskildsen, & Pedersen, 2007).

Institutional review boards (IRBs) at both recruitment sites approved the protocol. Surrogates provided written consent; we approached patients for assent or consent based on a brief cognitive assessment. Nurse-led ETM was not the standard of care during the study period nor was it common to consult physical therapists; there were no unit-based physical therapists delivering mobility screening or rehabilitation.

Setting

Two academic medical centers and four ICUs comprised the settings. All ICUs were closed or modified closed, with an intensivist providing daily assessment and interventions.

Sample

We screened for enrollment consecutive patients not enrolled in another study, who received MV for 36 hr and were expected to require ≥ 24 hr more of MV. Exclusion criteria were a length of ICU stay of 14 or more days prior to eligibility to enroll, a weight greater than 350 lb because we did not have access to specialized bariatric equipment for mobility, a history or acute diagnosis of neurological or orthopedic injury that precluded the ability to participate in volitional and progressive ETM (e.g., new spinal cord injury, delayed lower extremity fracture repair, inability to follow directions due to a chronic brain condition such as severe dementia or stroke/hypoxic coma, or related conditions), new myocardial infarction, the presence of open fascia from abdominal or lower extremity surgery (e.g., fasciotomy for infection), or end-stage or end-of-life treatment (e.g., hospice consulted) or intensivist opinion that the individual was moribund. We also excluded patients without a surrogate or with a surrogate who could not be contacted over a 2-day period.

We assigned patients to frequency groups via a random number assignment drawn from an opaque envelope. Participants with even numbers received once-daily ETM, while those with odd numbers received the intervention twice daily. Participants received the first intervention after 48 hr or more of MV occurred.

Sample Size

We determined sample size needed to explore whether cytokines were altered by the dose of ETM. We estimated that a sample size of 50 would have .80 power to detect a .30 effect size with an α of .10, using Analysis of Covariance (ANCOVA) repeated measures both within and between interactions (Faul et al., 2007). The effect size used in this calculation was larger than what we had obtained in an earlier study (Winkelman, Johnson, & Gordon, 2015); we anticipated fewer missed interventions and greater dose from twice-daily completion leading to a greater effect. We selected a larger α value due to the established safety of the intervention (Morris et al., 2008; Winkelman et al., 2012).

Procedures

Trained registered nurses (RNs) delivered the ETM intervention. The first activity was started after informed consent (and, when appropriate, patient assent) was obtained and the patient demonstrated stability based on the following criteria: at least 2 hr of systolic blood pressure >90 and <165 mmHg (mean arterial pressure 60–90 mmHg), heart rate 58–110 beats per min, respiratory rate <28 breaths per min, fraction of inspired oxygen (FiO₂) $<60\%$, and positive end-expiratory pressure

< 7.5 cmH₂O. In addition, no new or upward titration of vaso-pressors or antidysrhythmics should have occurred in the 4 hr preceding the intervention. Patients with a fever spike in the hour preceding the first planned daily activity received no intervention.

We collected blood daily for up to 3 contiguous study days following a period of rest and a period of ETM and then weekly or on the day of ICU discharge ($\pm$ 24 hr). A lab technician blinded to the intervention analyzed the serum. A trained RN blinded to the frequency and intensity of the ETM activity collected measures of delirium and muscle strength (described below) during the only or last period of ETM daily for up to 5 contiguous days, then weekly, and on the day of ICU discharge.

Measures

Serum biomarkers were measured using a Meso Scale Discovery multiplex platform, following manufacturer guidelines to attain accuracy (www.mesocale.com, 2011). Trained staff in the Dahms Clinical Research Unit (UL1TR 000439-06) completed analyses in a batch process. We assessed participants for muscle strength with the Manual Muscle Test (MMT, Medical Research Council) Scale using the ICU-acquired weakness protocol (De Jonghe et al., 2002; Fan et al., 2014). To assess handgrip strength, we used a dynamometer and a previously published protocol (Ali et al., 2008). We measured delirium in late afternoon, after completing all ETM, using the Confusion Assessment Method-ICU (CAM-ICU; Ely et al., 2001). MV duration was measured in days such that whenever more than 12 hr of MV in a 24-hr period (beginning at 12 midnight) was documented, we counted that as 1 day. We calculated the LOS in the ICU on the day of discharge. We trained data collectors for collection of chart data and outcome assessments prior to the study and retrained them as needed to maintain intra- and interrater reliability >95%. Outcome assessors (duration of MV, ICU LOS, MMT, handgrip, and CAM-ICU) were RNs who were blinded to the intervention. We managed data using REDCap, Version 7.0 electronic data capture tools (Harris et al., 2009) and exported them to a spreadsheet for analyses using SPSS Statistics for Windows, Version 21(IBM).

Analysis

We summarized and compared participants' characteristics for each study arm using a *t* test, Wilcoxon–Mann–Whitney test, or proportion test, as appropriate. To study the longitudinal effects of the intervention on the biomarkers or outcome variables, we used the generalized estimating equation method based on intention to treat rather than actual delivery (i.e., actual delivery could be 0, 1, or 2 times daily). We entered “time” (i.e., Days 1, 2, and 3 of intervention) into all adjusted analyses, as this was a repeated measures analysis. We assumed that the repeated measurements followed exchangeable correlation structure and used the robust method to calculate standard errors of the estimates. After examining the demographic and related variables for significant (i.e., $p \leq .25$) correlations, we

built statistical models by including time and significant covariates. For all of the computations, we used statistical software Stata, Version 13.0 (Stata).

Because this study was exploratory and hypothesis generating (similar to a Phase II trial), we used a significance level of 10% for all hypothesis tests (Rubinstein et al., 2005). However, as per the American Statistical Association statement on *p* values, we also report nonzero β coefficients, 95% confidence intervals, and clinical relevance as appropriate (Wasserstein & Lazar, 2016).

Results

We recruited a total of 55 patients, randomizing 29 of these to once-daily ETM and the remainder to twice-daily ETM from December 2009 to December 2012. One participant asked to be withdrawn during an assent process, and we did not include that participant's data in the analyses. Thus, the total number of participants for this report is 54, detailed in Figure 1. No adverse events occurred during the intervention (see Online Supplemental Information about Adverse Events From ETM and Complications From Immobility).

Sample

We report the demographic characteristics of participants in Table 1. Participants remained in the study for an average of 4 days (range 1–30). Online Supplemental Figure S1 displays a description of the ETM intervention delivered in each group. A total of six participants were unable to complete the study due to physiological deterioration (typically new-onset sepsis) after 2–7 days of the intervention. We have included their data up to the day of withdrawal for deterioration in this report. As shown in Table 1, there were no significant differences in the demographic characteristics of individuals randomized to once-daily ETM compared to those enrolled in twice-daily ETM.

All participants receiving moderate-intensity ETM achieved sitting at the edge of the bed. Approximately 20% of the moderate-intensity activity included an active stand and pivot transfer to the chair. Only 10% of all activities in this category included walking 8 feet or more.

Biomarkers

We report the overall mean and median resting and activity serum biomarker results in Online Supplemental Table S2. Online Supplemental Table S3 details biomarkers by frequency of the intervention, while Online Supplemental Table S4 details mean values of biomarkers by the intensity of the intervention. There were no significant differences in baseline values for any of the inflammatory biomarkers, comparing the arms of the study ($p > .05$).

Adherence to the Intervention

Table 1 reports the number of potential ETM sessions and the number of sessions completed per participant by intervention—

Figure 1. Diagram illustrating enrollment procedures.

frequency group. All intervention sessions occurred over a minimum of 20 continuous minutes. Participants did not complete approximately 20% of ETM sessions were not completed, a similar value in both arms ($\chi^2 = .2$, $p = .35$). The most common reason for missing an ETM session was deterioration in patient status (e.g., unstable hemodynamics, fever, or increase in FiO_2) near the time of planned intervention. For six patients, ongoing instability resulted in discontinuing study participation because no interventions occurred for at least 36 hr. Another recurrent reason ($n = 7$) for not delivering ETM was conflict with medical procedures (e.g., tracheostomy placement, transport to imaging test, or other). Several patients ($n = 8$) declined to participate in a session.

Fewer than 25% of participants received ETM for 7 or more days due to transfer out of the ICU setting ($n = 12$ for 7 days, $n = 4$ for 14 days, and $n = 2$ for 15–30 days). There were insufficient data to evaluate biomarkers and outcomes following the initial 3 days of ETM. In regard to safety and the ETM intervention, no serious adverse events occurred during ETM. We report more detail about adverse events measured and a narrative summary of these negative findings in Online Supplemental Information about Adverse Events From ETM and Complications From Immobility.

Associations of Levels of Inflammatory Serum Biomarkers (IL-6, 8, 10, and 15; TNF- α) With Frequency of ETM

We report the adjusted analyses of IL-6, IL-8, IL-10, IL-15, and TNF- α and frequency of ETM in Table 2. While TNF- α level was significantly and negatively associated with frequency, the confidence intervals include 0, indicating that the hypothesis

that more frequent ETM would decrease levels of pro-inflammatory biomarkers was not supported in this sample.

Associations of Selected Patient Outcomes of Systemic Health With Frequency of ETM

We analyzed the outcomes of duration of MV, ICU LOS, and muscle strength (MMT or handgrip) and delirium for significance by frequency of ETM delivery and report results in Table 3. Only ICU LOS was consistently and significantly reduced for patients who received ETM twice daily compared to those who received it once daily (i.e., 13.40 vs. 18.76 ICU days; $p < .10$).

Associations of Inflammatory Serum Biomarkers (IL-6, 8, 10, and 15; TNF- α) With ETM Intensity

In Table 4, we report the adjusted analyses of IL-6, IL-8, IL-15, TNF- α , and IL-10 levels and intensity of ETM. There were no significant findings for the association of inflammatory biomarkers with intensity of ETM.

Associations Between Selected Patient Outcomes of Systemic Health With ETM Intensity

Table 5 summarizes the system-level health outcomes by intensity. Both MMT scores and dynamometer handgrip values were greater on Days 1 and 3 among participants who received moderate-intensity ETM compared to those who received low-intensity ETM ($p < .10$). There was also reduced delirium on both Days 1 and 3 for participants who received moderate-intensity

Table 1. Sample Characteristics and Delivery of the ETM Intervention.

Characteristic	ETM Intervention Frequency		<i>p</i> Value ^a
	Once Daily (<i>n</i> = 29)	Twice Daily (<i>n</i> = 25)	
	Mean $\pm$ SD or <i>n</i> (%)	Mean $\pm$ SD or <i>n</i> (%)	
Age (years)	59.48 $\pm$ 15.56	52.68 $\pm$ 18.53	.15
Sex, female	18 (62.1)	11 (44.0)	.18
Race			
Caucasian	24 (82.8)	20 (80.0)	.28
African American	3 (10.3)	5 (20.0)	
Hispanic	2 (6.9)	0 (0.0)	
Body mass index (kg/m ²)	29.55 $\pm$ 6.99	31.10 $\pm$ 11.07	.53
Survived	28 (96.6)	21 (84.0)	.11
Diagnosis type			
Pulmonary	12 (41.4)	11 (44.0)	
Cardiovascular	9 (31.0)	2 (8.0)	.16
Renal	0 (0.0)	1 (4.0)	
Gastrointestinal	3 (10.3)	2 (8.0)	
Other	5 (17.2)	9 (36.0)	
P/F ratio at ICU admission	206.14 $\pm$ 111.64	201.46 $\pm$ 136.05	.69
SOFA at ICU admission	7.28 $\pm$ 4.02	6.24 $\pm$ 3.19	.41
APACHE III	71.86 $\pm$ 34.12	64.40 $\pm$ 23.77	.57
Charlson comorbidity index ^b	1.28 $\pm$ 1.22	1.44 $\pm$ 1.50	.88
Number of comorbidities	3.55 $\pm$ 2.26	3.00 $\pm$ 2.75	.34
ICU day enrolled	7.79 $\pm$ 4.11	7.60 $\pm$ 6.47	.18
Delivery of ETM			
Opportunities for ETM sessions/subject	7.03 $\pm$ 5.41	9.28 $\pm$ 4.72	.02
Completed ETM sessions/subject	5.79 $\pm$ 4.65	7.52 $\pm$ 4.39	.03
Proportion of planned/delivered ETM sessions per subject	79%	81%	.61

Note. APACHE III = Acute Physiology and Chronic Health Evaluation III; ETM = early therapeutic mobility; ICU = intensive care unit; P/F ratio = partial pressure of oxygen in arterial blood/fraction of inspired oxygen; SOFA = sequential organ failure assessment.

^aDepending on the data measured or distribution, we performed *t* test, Wilcoxon rank sum test, or χ^2 test.

^bThe original scale (Charlson et al., 1987) was used in this study, as the revised version did not come out until the study was well underway.

ETM compared to those who received a maximum low-intensity ETM intervention (*p* < .10).

Discussion

In the present study, we examined associations between levels of biomarkers and patient outcomes and once- versus twice-daily ETM led by RNs. In terms of feasibility, the RNs were able to deliver the ETM intervention either once or twice daily for the majority (80%) of sessions planned. This delivery rate is similar to those of other research reports and may reflect a high

Table 2. Associations Between ETM Frequency (Once Vs. Twice Daily) and Levels of Inflammatory Biomarkers.

Biomarker	Regression Coefficient, $\hat{\beta}$ (SE)	95% Confidence Interval of $\hat{\beta}$	
		Lower Limit	Upper Limit
IL-6 ^a	−1.39 (4.31)	−9.83	7.05
IL-8 ^b	−7.49 (3.35)	−14.06	−0.92
IL-10 ^c	0.35 (0.62)	−0.87	1.56
IL-15 ^d	0.01 (0.33)	−0.67	0.66
TNF- α ^e	−0.17 (0.09)	−0.35	0.01

Note. IL = interleukin; TNF = tumor necrosis factor.

^aAnalysis was adjusted for significant (in an unadjusted analysis) covariates race, body mass index, partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F ratio), C-reactive protein (CRP), and time.

^bAnalysis was adjusted for significant covariates sex, delirium, and time.

^cAnalysis was adjusted for significant covariates P/F ratio and time.

^dAnalysis was adjusted for significant covariates comorbidity prognostics and time.

^eAnalysis was adjusted for significant covariates CRP and time.

Table 3. Associations Between Frequency of ETM and Outcomes.

Outcome	ETM Intervention Frequency		<i>p</i> Value
	Once Daily (<i>n</i> = 29)	Twice Daily (<i>n</i> = 25)	
	Mean $\pm$ SD or <i>n</i> (%)	Mean $\pm$ SD or <i>n</i> (%)	
Duration of mechanical ventilation (days)	12.86 $\pm$ 7.17	10.40 $\pm$ 6.39	.12
ICU length of stay (days)	18.76 $\pm$ 14.47	13.40 $\pm$ 7.97	.06
Day 1 manual muscle test (total score)	26.00 $\pm$ 19.87	34.56 $\pm$ 19.65	.20
Day 1 dynamometer handgrip (Nm)	37.92 $\pm$ 30.50	27.85 $\pm$ 38.33	.17
Day 3 manual muscle test (total score)	38.10 $\pm$ 19.22	36.15 $\pm$ 15.91	.67
Day 3 dynamometer handgrip (Nm)	25.12 $\pm$ 27.76	27.45 $\pm$ 24.64	.68
Day 1 delirium positive	20 (69.0)	11 (44.0)	.11
Day 3 delirium positive	9 (52.38)	8 (47.06)	.80

Note. ETM = early therapeutic mobility; ICU = intensive care unit.

value placed on ETM by the interventionist and staff nurses who delivered the intervention (Connolly et al., 2017; Granger et al., 2017). There were no significant associations between levels of inflammatory biomarkers and frequency of ETM. Among health outcomes, ICU LOS was reduced by an average of 5.36 days for patients who received twice-daily ETM compared with those who received the intervention once a day.

Regarding our secondary purpose, to examine the effects of the intensity of ETM (low/in-bed vs. moderate/out-of-bed) on biomarkers and outcomes, we did not have significant findings related to biomarkers. Patients receiving a moderate-intensity ETM intervention were more likely to achieve sitting at the edge of the bed than those receiving low-intensity ETM. There

Table 4. Associations Between ETM Intensity and Levels of Inflammatory Biomarkers.

Biomarkers	Regression Coefficients		95% Confidence Interval of β	
	Low Intensity, $\hat{\beta}_1$ (SE)	Moderate Intensity, $\hat{\beta}_2$ (SE)	Low Intensity	Moderate Intensity
IL-6 ^a	0.68 (8.77)	-4.61 (8.94)	-16.52-17.87	-22.14-12.92
IL-8 ^b	8.26 (4.30)	2.84 (3.28)	-0.18-16.70	-3.59-9.26
IL-10 ^c	-2.09 (1.74)	-1.31 (1.73)	-5.50-1.32	-4.70-2.08
IL-15 ^d	0.93 (0.75)	0.92 (0.61)	-0.54-2.40	-0.28-2.12
TNF- α ^e	0.17 (0.13)	0.11 (0.13)	-0.09-0.43	-0.16-0.39

Note. Possible activity intensities were low intensity, or in-bed activity, versus moderate intensity or activity completed while sitting at edge of bed or out of bed. ETM = early therapeutic mobility

^aAnalysis was adjusted for significant (in an unadjusted analysis) covariates race, body mass index, partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F ratio), C-reactive protein (CRP), and time.

^bAnalysis was adjusted for significant covariates sex, delirium, and time.

^cAnalysis was adjusted for significant covariates P/F ratio and time.

^dAnalysis was adjusted for significant covariates comorbid prognostics and time. ^eAnalysis was adjusted for significant covariates CRP and time.

Table 5. Associations Between ETM Intensity and System-Level Health Outcomes.

Outcome Measure	Low Intensity (n = 35)	Moderate Intensity (n = 19)	p Value
	Mean (SD) or n (%)	Mean (SD) or n (%)	
Duration of MV (days)	12.66 $\pm$ 7.43	10.00 $\pm$ 5.47	.177
ICU length of stay (days)	17.51 $\pm$ 13.31	14.00 $\pm$ 9.41	.313
Day 1 MMT (total score)	18.24 $\pm$ 15.24	45.33 $\pm$ 14.46	<.001
Day 3 MMT (total)	28.68 $\pm$ 16.44	51.20 $\pm$ 6.69	<.001
Day 1 dynamometer handgrip (Nm)	14.11 $\pm$ 17.86	46.17 $\pm$ 38.61	.024
Day 3 dynamometer handgrip	14.69 $\pm$ 17.56	36.18 $\pm$ 28.28	.026
Day 1 delirium positive	25 (80.65)	6 (19.35)	.003
Day 3 delirium positive	16 (94)	1 (5.88)	.007

Note. ETM = early therapeutic mobility; ICU = intensive care unit; MMT = manual muscle test; MV = mechanical ventilation.

were associations of greater muscle strength (measured by both MMT and dynamometer handgrip) and reduced delirium with the performance of activity categorized as moderate on Days 1 and 3 of the intervention.

ICU LOS was reduced by $\geq 20\%$ in participants who received twice-daily ETM compared to those who received a once-daily intervention, implying clinical importance. Other reports and meta-analyses in the literature suggest that low-frequency (once daily) and relatively low-intensity ETM reduces MV days and ICU LOS (Castro-Avila, Seron, Fan, Gaete, & Mickan, 2015; Kayambu, Boots, & Paratz, 2013; Kayambu et al., 2015; Kress & Hall, 2014; Morris et al., 2008; Sosnowski, Lin, Mitchell, & White, 2015), but these findings have not been consistent across studies (Morris

et al., 2016; Moss et al., 2016). It is important to note that the community in which we conducted the present study had five long-term acute care hospitals, and it was uncommon for a stable ventilated patient to stay in an ICU for longer than 10–14 days during the study period.

Both greater MMT and handgrip values were associated with moderate-intensity ETM in the sample, a finding contrary to a recent meta-analysis of any intervention for early rehabilitation (Castro-Avila et al., 2015). Our results suggest that ETM interventions with moderate intensity are necessary to preserve muscle strength in critically ill adults. Other multi-study evaluations have suggested that moderate-intensity ETM could decrease the severity of ICU-acquired muscle weakness and dysfunction (Castro-Avila et al., 2015; Hermans & Van den Berghe, 2015; Sosnowski et al., 2015). Our finding may reflect improved muscle recruitment by the central nervous system related to decreased delirium. It may be that both upright positioning associated with moderate-intensity ETM and clinician interaction stimulate the central nervous system, ultimately allowing individuals to deliver more effective effort in ETM. Our results are reported as association; we did not randomize intensity of ETM to subjects.

Delirium had an inverse association with moderate-intensity ETM on both Days 1 and 3 after enrollment. Delirium-negative patients were more likely to better follow directions and achieve moderate-intensity ETM than patients with delirium. Other reports about ETM support our finding of delayed onset of delirium in ICU adults who received systematic activity (Hager et al., 2013; Needham et al., 2010; Schweickert et al., 2009; Smith & Grami, 2017). A recent study also suggested that range of motion is insufficient to prevent delirium among older adults (Karadas & Ozdemir, 2017). Although we did not time our ETM intervention to occur with a sedation interruption, fewer than 15% of our study participants were receiving continuous sedation at enrollment (data not reported); none received continuous sedation on Day 3 following enrollment. Previous authors have recommended combining ETM with sedation vacation as best practice to delay the onset and severity of delirium (Brummel & Girard, 2013).

Our intervention in the present study might not be considered “early,” with the first session occurring typically on Day 7 after ICU admission. No single definition of “early mobility” exists (Hashem, Nelliot, & Needham, 2016; Moss et al., 2016). In this project, ETM occurred on the first day that a patient met enrollment criteria, and we used daily assessments to progressively increase the intensity of the intervention. Early mobility thus started as soon as the patient’s crisis of health stabilized but before the critical illness resolved. Our data suggest that ETM is feasible and safe (refer to Online Supplemental Information about Adverse Events) as a nurse-led intervention and can be delivered twice daily in an ICU.

Limitations

We did not have access to baseline muscle strength or function for any participant, so we cannot be confident that we delivered

“exercise” or a dose of activity that was congruent with baseline strength or ability. We did design the intervention as systematic activity to sustain or improve health, congruent with the domain “exercise” (Maitin, 2015). Improvement in muscle strength might have been due to preadmission variations (e.g., patients who were stronger at baseline were more likely to improve). However, given the similarity in sample characteristics of age, gender, severity of illness (i.e., Acute Physiology and Chronic Health Evaluation III score, Gocmen et al., 2007; partial pressure of oxygen in arterial blood to fraction of inspired oxygen at ICU admission and number and severity of comorbidities, Charlson, Pompei, Ales, & MacKenzie, 1987), and random assignment to the frequency of the intervention, participants had similar potential for preexisting weakness impacting measures. Our sample size was small, physiologically stable, and diverse in diagnoses. There were wide ranges of values for many variables, especially in the biomarkers. This heterogeneity may have influenced results. We did not use resistance exercise in our intervention on the advice of one IRB panel. It may be that adding resistance to in-bed or low-intensity exercise would alter results. We did not have a control group of patients who received no ETM; our approach reflects a pragmatic approach consistent with safe practice (i.e., screening for safety prior to initiating mobility) rather than a clinical trial approach. The study was not powered for secondary analyses, so findings may be spurious. Nonetheless, associations between muscle strength and delirium outcomes among patients who received moderate-intensity ETM were significant and changed over time.

Conclusion

Changes in inflammatory biomarkers were not associated with either frequency or intensity of ETM in this study. There were clinically important decrements in ICU LOS among patients who received twice-daily ETM. Increased muscle strength and decreased delirium were associated with moderate-intensity ETM. This study provides support for further investigation of the therapeutic dose for ETM.

Author Contributions

Chris Winkelman contributed to conception, design, acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Abdus Sattar contributed to analysis and interpretation; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Hasina Momotaz contributed to analysis and interpretation; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Kimberly D. Johnson contributed to acquisition and interpretation; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Peter Morris contributed to conception and analysis; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. James R. Rowbottom contributed to conception; critically

revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. John Daryl Thornton contributed to conception; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Sheryl Feeney contributed to acquisition; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. Alan Levine contributed to design; critically revised manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Financial support for this study included the following: National Institutes of Health (NIH): ICU Mobility 1R21 NR10781-01A1. Blood samples were stored at the laboratory of the MetroHealth Clinical and Translation Science Collaborative (CTSC), NIH Funding UL1 TR00439. Blood samples were also stored and analyzed at the Dahms Clinical Unit laboratory at UHMC, NIH Funding UL1TR 00439-06. Study data were collected and managed using REDCap electronic data capture tools hosted at the University Hospital's Cleveland Medical Center (UHMC). <http://ClinicalTrials.gov> Identifier: NCT00999011.

ORCID iD

Chris Winkelman <http://orcid.org/0000-0002-2988-9304>

Supplemental Material

Supplemental material for this article is available online.

References

- Ali, N. A., O'Brien, J. M. Jr., Hoffmann, S. P., Phillips, G., Garland, A., Finley, J. C., ... Marsh, C. B. (2008). Acquired weakness, handgrip strength, and mortality in critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, 178, 261–268.
- Astrom, M. B., Feigh, M., & Pedersen, B. K. (2010). Persistent low-grade inflammation and regular exercise. *Frontiers in Bioscience*, 2, 96–105.
- Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gelinas, C., Dasta, J. F., ... Jaeschke, R. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine*, 41, 263–306.
- Brummel, N. E., & Girard, T. D. (2013). Preventing delirium in the intensive care unit. *Critical Care Clinics*, 29, 51–65.
- Castro-Avila, A. C., Seron, P., Fan, E., Gaete, M., & Mickan, S. (2015). Effect of early rehabilitation during intensive care unit stay on functional status: Systematic review and meta-analysis. *PLoS One*, 10, e0130722.
- Cerejeira, J., Firmino, H., Vaz-Serra, A., & Mukaetova-Ladinska, E. B. (2010). The neuroinflammatory hypothesis of delirium. *Acta Neuropathologica*, 119, 737–754.
- Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in

- longitudinal studies: Development and validation. *Journal of Chronic Diseases*, 40, 373–383.
- Connolly, B. A., Mortimore, J. L., Douiri, A., Rose, J. W., Hart, N., & Berney, S. C. (2017). Low levels of physical activity during critical illness and weaning: The evidence-reality gap. *Journal of Intensive Care Medicine*, 885066617716377. Advance online publication. doi:10.1177/0885066617716377
- De Jonghe, B., Sharshar, T., Lefaucheur, J. P., Authier, F. J., Durand-Zaleski, I., Boussarsar, M., . . . Bastuji-Garin, S. (2002). Paresis acquired in the intensive care unit: A prospective multicenter study. *Journal of the American Medical Association*, 288, 2859–2867.
- Ely, E. W., Inouye, S. K., Bernard, G. R., Francis, J., May, L., Truman, B., . . . Dittus, R. (2001). Delirium in mechanically ventilated patients: Validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Journal of the American Medical Association*, 286, 2703–2710.
- Fan, E. (2012). Critical illness neuromyopathy and the role of physical therapy and rehabilitation in critically ill patients. *Respiratory Care*, 57, 933–944; discussion 944–936.
- Fan, E., Cheek, F., Chlan, L., Gosselink, R., Hart, N., Herridge, M. S., . . . Ali, N. A. (2014). An official American thoracic society clinical practice guideline: The diagnosis of intensive care unit-acquired weakness in adults. *American Journal of Respiratory and Critical Care Medicine*, 190, 1437–1446.
- Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39, 175–191.
- Fischer, C. P., Berntsen, A., Perstrup, L. B., Eskildsen, P., & Pedersen, B. K. (2007). Plasma levels of interleukin-6 and C-reactive protein are associated with physical inactivity independent of obesity. *Scandinavian Journal of Medicine & Science in Sports*, 17, 580–587.
- Girard, T. D., Alhazzani, W., Kress, J. P., Ouellette, D. R., Schmidt, G. A., Truitt, J. D., . . . Morris, P. E. (2017). An official American thoracic society/American college of chest physicians clinical practice guideline: Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. *American Journal of Respiratory and Critical Care Medicine*, 195, 120–133.
- Gocmen, E., Klc, Y. A., Yoldas, O., Ertan, T., Karakose, N., Koc, M., & Tez, M. (2007). Comparison and validation of scoring systems in a cohort of patients treated for biliary acute pancreatitis. *Pancreas*, 34, 66–69.
- Goldhammer, E., Tanchilevitch, A., Maor, I., Beniamini, Y., Rosenschein, U., & Sagiv, M. (2005). Exercise training modulates cytokines activity in coronary heart disease patients. *International Journal of Cardiology*, 100, 93–99.
- Grander, W., Dunser, M., Stollenwerk, B., Siebert, U., Dengg, C., Koller, B., . . . Tilg, H. (2010). C-reactive protein levels and post-ICU mortality in nonsurgical intensive care patients. *Chest*, 138, 856–862.
- Granger, C. L., Connolly, B., Denehy, L., Hart, N., Antippa, P., Lin, K. Y., & Parry, S. M. (2017). Understanding factors influencing physical activity and exercise in lung cancer: A systematic review. *Supportive Care in Cancer*, 25, 983–999.
- Hager, D. N., Dinglas, V. D., Subhas, S., Rowden, A. M., Neufeld, K. J., Bienvenu, O. J., . . . Needham, D. M. (2013). Reducing deep sedation and delirium in acute lung injury patients: A quality improvement project. *Critical Care Medicine*, 41, 1435–1442.
- Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, 42, 377–381.
- Hashem, M. D., Nelliot, A., & Needham, D. M. (2016). Early mobilization and rehabilitation in the ICU: Moving back to the future. *Respiratory Care*, 61, 971–979. doi:10.4187/respcare.04741
- Hermans, G., & Van den Berghe, G. (2015). Clinical review: Intensive care unit acquired weakness. *Critical Care*, 19, 274.
- Karadas, C., & Ozdemir, L. (2017). The effect of range of motion exercises on delirium prevention among patients aged 65 and over in intensive care units. *Geriatric Nursing*, 37, 180–185.
- Kayambu, G., Boots, R., & Paratz, J. (2013). Physical therapy for the critically ill in the ICU: A systematic review and meta-analysis. *Critical Care Medicine*, 41, 1543–1554.
- Kayambu, G., Boots, R., & Paratz, J. (2015). Early physical rehabilitation in intensive care patients with sepsis syndromes: A pilot randomised controlled trial. *Intensive Care Medicine*, 41, 865–874.
- Kress, J. P., & Hall, J. B. (2014). ICU-acquired weakness and recovery from critical illness. *New England Journal of Medicine*, 370, 1626–1635.
- Maitin, I. (2015). *Current diagnosis and treatment: Physical medicine and rehabilitation*. New York, NY: McGraw-Hill.
- Morris, P. E., Berry, M. J., Files, D. C., Thompson, J. C., Hauser, J., Flores, L., . . . Young, M. P. (2016). Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: A randomized clinical trial. *Journal of the American Medical Association*, 315, 2694–2702.
- Morris, P. E., Goad, A., Thompson, C., Taylor, K., Harry, B., Passmore, L., . . . Haponik, E. (2008). Early intensive care unit mobility in the treatment of acute respiratory failure. *Critical Care Medicine*, 36, 2238–2243.
- Moss, M., Nordon-Craft, A., Malone, D., Van Pelt, D., Frankel, S. K., Warner, M. L., . . . Schenkman, M. (2016). A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. *American Journal of Respiratory and Critical Care Medicine*, 193, 1101–1110.
- Needham, D. M., Korupolu, R., Zanni, J. M., Pradhan, P., Colantuoni, E., Palmer, J. B., . . . Fan, E. (2010). Early physical medicine and rehabilitation for patients with acute respiratory failure: A quality improvement project. *Archives of Physical Medicine and Rehabilitation*, 91, 536–542.
- Nydahl, P., Sricharoenchai, T., Chandra, S., Kundt, F. S., Huang, M., Fischill, M., & Needham, D. M. (2017). Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. *Annals of the American Thoracic Society*, 14, 766–777.
- Pandharipande, P. P., Girard, T. D., Jackson, J. C., Morandi, A., Thompson, J. L., Pun, B. T., . . . Investigators, B.-I. S. (2013).

- Long-term cognitive impairment after critical illness. *New England Journal of Medicine*, 369, 1306–1316.
- Pedersen, B. K. (2000). Exercise and cytokines. *Immunology and Cell Biology*, 78, 532–535.
- Pedersen, B. K. (2011a). Exercise-induced myokines and their role in chronic diseases. *Brain, Behavior, & Immunity*, 25, 811–816.
- Pedersen, B. K. (2011b). Muscles and their myokines. *Journal of Experimental Biology*, 214, 337–348.
- Rubinstein, L. V., Korn, E. L., Freidlin, B., Hunsberger, S., Ivy, S. P., & Smith, M. A. (2005). Design issues of randomized phase II trials and a proposal for phase II screening trials. *Journal of Clinical Oncology*, 23, 7199–7206.
- Schweickert, W. D., Pohlman, M. C., Pohlman, A. S., Nigos, C., Pawlik, A. J., Esbrook, C. L., . . . Kress, J. P. (2009). Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet*, 373, 1874–1882.
- Smith, C. D., & Grami, P. (2017). Feasibility and effectiveness of a delirium prevention bundle in critically ill patients. *American Journal of Critical Care*, 26, 19–27.
- Sosnowski, K., Lin, F., Mitchell, M. L., & White, H. (2015). Early rehabilitation in the intensive care unit: An integrative literature review. *Australian Critical Care*, 28, 216–225. doi:10.1016/j.aucc.2015.05.002
- Truong, A. D., Fan, E., Brower, R. G., & Needham, D. M. (2009). Bench-to-bedside review: Mobilizing patients in the intensive care unit—from pathophysiology to clinical trials. *Critical Care Forum*, 13, 216–224.
- Wasserstein, R. L., & Lazar, N. L. (2016). The ASA's statement on p-values: Context, process, and purpose. *American Statistician*, 70, 129–133.
- Winkelman, C. (2013). Mechanisms for muscle health in the critically ill patient. *Critical Care Nursing Quarterly*, 36, 5–16.
- Winkelman, C., Johnson, K. D., & Gordon, N. (2015). Associations between muscle-related cytokines and selected patient outcomes in the ICU. *Biological Research for Nursing*, 17, 125–134.
- Winkelman, C., Johnson, K. D., Hejal, R., Gordon, N. H., Rowbottom, J., Daly, J., . . . Levine, A. D. (2012). Examining the positive effects of exercise in intubated adults in ICU: A prospective repeated measures clinical study. *Intensive and Critical Care Nursing*, 28, 307–318.
- Witteveen, E., Wieske, L., van der Poll, T., van der Schaaf, M., van Schaik, I. N., Schultz, M. J., . . . Horn, J. (2017). Increased early systemic inflammation in ICU-acquired weakness; A prospective observational cohort study. *Critical Care Medicine*, 45, 972–979.