Clinical trials of early mobilization of critically ill patients

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Intensive care unit-acquired weakness is a common complication of critical illness leading to severe functional impairment in many intensive care unit survivors. Critically ill patients who require mechanical ventilation are routinely immobilized for prolonged time periods. This immobilization is exacerbated by frequent administration of sedative agents. Recently, several investigators have described the feasibility and potential benefits of mobilizing mechanically ventilated intensive care unit patients. Such an intervention requires a multidisciplinary team approach to patient care, involving nursing, physical therapy, occupational therapy, and respiratory therapy practitioners. Recent studies of early mobilization of mechanically ventilated intensive care unit patients have noted this intervention to be safe and associated with improved functional outcomes in this extremely ill patient cohort. Such outcomes include high percentages of patients able to ambulate on intensive care unit and hospital discharge and shortened hospital length of stay. With preliminary studies demonstrating remarkable feasibility and successes, further prospective studies of early mobilization are needed to evaluate this intervention. (Crit Care Med 2009; 37[Suppl.]:S442–S447)

Key Words: mechanical ventilation; clinical protocols; physical therapy; occupational therapy; mobilization; ICU-acquired weakness; critical illness myopathy; muscle atrophy; intensive care unit; neuropathy; sedation

Critically ill patients frequently present with an extreme derangement of physiologic homeostasis, leading intensive care unit (ICU) care to focus on recovery from acute organ system failure. Those organ systems whose failure threatens survival (e.g., cardiovascular, pulmonary, renal) accordingly receive greatest attention in the ICU. Patients requiring mechanical ventilation are among the most challenging in this regard. In the midst of ICU care, with its focus on resuscitation and survival, there is customarily little early attention toward neuromuscular function. However, recent work on outcomes in ICU survivors has recognized that these patients suffer profound and persistent impairments in physical function, with recovery that is typically slow and incomplete (1–5). In 109 patients studied 1 yr after recovering from acute respiratory distress syndrome, Herridge and colleagues noted that every patient reported poor function, which was attributed to loss of muscle bulk, proximal muscle weakness, and fatigue (1). Only half of the patients in this cohort were employed 1 yr after recovery, and the reported reasons for continued unemployment included persistent fatigue, weakness, and poor functional status (e.g., footdrop and large joint immobility). De Jonghe and colleagues described a 25% prevalence of ICU-acquired weakness in a cohort of 95 patients receiving mechanical ventilation (6). The study described independent predictors of ICU-acquired weakness, which included duration of mechanical ventilation, days of multiple system organ failure, corticosteroid administration, and female gender.

As clinical recovery from critical illness and respiratory failure describes severe physical deconditioning accompanied by weight loss, profound weakness, and functional impairment (1, 2, 7, 8), a growing body of literature recounts neuropathies and myopathies described categorically as “ICU-acquired weakness” (9). Although the mechanisms are poorly understood (10), preliminary evidence suggests that muscle injury from systemic inflammation (11, 12), along with deconditioning from immobility (13, 14), may be important. Catabolism with skeletal muscle proteolysis and atrophy are frequently seen in ICU patients and also may contribute to ICU-acquired weakness.

To date, there are only limited data suggesting that physical activity may attenuate neuromuscular weakness in critical illness (14). Griffiths et al described the effects of continuous passive motion of one leg in critically ill patients with respiratory failure during neuromuscular blockade, with the contralateral leg serving as a control (14). Muscle fiber atrophy was prevented by this intervention in those with high illness severity. Muscle DNA to protein ratios (an index of wasting) and muscle protein content were reduced less profoundly in the leg receiving continuous passive motion. Other studies described the detriments of prolonged immobility in mechanically ventilated ICU patients (15, 16), and many have speculated on the potential benefits of physical activity in sedentary ICU patients (17–22).

Many mechanically ventilated patients receive sedative and analgesic drugs, often in high doses, predisposing them to prolonged periods of unconsciousness and immobility. Previous work has identified excessive ICU sedation as an important cause of prolonged mechanical ventilation and ICU length of stay (23–25). Kress et al previously reported that a strategy of daily interruption of sedative infusions in mechanically ventilated ICU patients significantly reduced ventilation time and ICU length of stay (25, 26). Accordingly, strategies that titrate sedative doses downward (24, 27) are used widely for the current management of mechanically ventilated patients.

Recently, there has been an interest in physical mobilization of ICU patients requiring mechanical ventilation. Mobilization...
tion during mechanical ventilation in the ICU requires patients to be awake and mentally "animated" (28). Accordingly, sedatives must be minimized and sedation protocols that allow patients to be awake and interactive must be utilized. De Jonghe and colleagues reported the impact of a sedation protocol utilizing the "adaptation to the ICU environment" instrument (Fig. 1) (29). This algorithm sought to maintain patients in a state where they were comfortable and tolerant yet awake and interactive. The adaptation to the ICU environment instrument has a "Consciousness" domain (with grades of "Awakeness" and "Comprehension" targeted) and a "Tolerance" domain (with grades of "Calmness," "Ventilator Synchrony," and "Face Relaxation" targeted). In a before-after trial comparing usual care with a sedation algorithm utilizing the adaptation to the ICU environment instrument (Fig. 2), the latter resulted in significantly fewer days of mechanical ventilation (4.4 vs. 10.3 days; \( p < 0.014 \)). Although the trial did not specifically utilize a mobilization protocol, patients subjected to the adaptation to the ICU environment sedation algorithm were noted to have significantly fewer pressure sores (18.6% vs. 37%; \( p = .04 \)). Because pressure sores are directly related to immobility in bed, this study suggests that a more mentally active, minimally sedated patient is more inclined to move around, even while confined to bed.

Bailey and colleagues reported the first trial of early mobilization in mechanically ventilated ICU patients (30). In a descriptive prospective cohort study, this group postulated that early mobilization after physiologic stabilization in the ICU might lead to patients accomplishing ambulation by the time of ICU discharge. This study targeted feasibility and safety as end points in a consecutive group of patients with respiratory failure admitted to the respiratory ICU at LDS Hospital in Salt Lake City, UT, over a 7-mo period. Patients mechanically ventilated for \( >4 \) days were eligible. Patients admitted to the LDS respiratory ICU were typically transferred from medical and shock trauma ICUs at LDS Hospital. As noted in Table 1, this group had high illness acuity in both the initial ICU and on transfer to the respiratory ICU. Mobilization began when patients demonstrated neurologic stability (i.e., response to verbal stimulation), respiratory stability (i.e., \( \text{FiO}_2 \leq 0.6 \) and positive end-expiratory pressure \( \leq 10 \text{ cm H}_2\text{O} \)), and circulatory stability (i.e., absence of orthostatic hypotension and catecholamine infusions), with an assessment for readiness occurring within 24 hrs of admission to the respiratory ICU. The protocol involved participation by a physical and respiratory therapist, nurse, and critical care technician. Three activities were targeted: sitting on the edge of the bed; sitting in a chair after bed transfer; and ambulating. The majority of patients admitted to this respiratory ICU came from other ICUs (94%), and the mean time to admission to this respiratory ICU was 10.5 ± 9.9 days. The investigators studied 103 patients undergoing 1449 activity events, which included 16% bed sitting, 31% chair sitting, and 53% ambulating. A total of 593 of the activity events occurred in intubated patients receiving wide ranges of \( \text{FiO}_2 \) (Fig. 3). Eighty-three percent of patients survived to hospital discharge with a median ambulation distance of 200 feet. At the end of the respiratory ICU stay, 2.4% of survivors accomplished no activity, 4.7% could sit on the edge of the bed, 15.3% could sit in a chair, 8.2% ambulated <100 feet, and 69.4% ambulated >100 feet. The investigators noted a very low adverse event occurrence rate, despite caring for patients with high illness acuity. One percent of activities had adverse events (five falls to knees without injury, four systolic

![Figure 1. Adaptation to the intensive care unit environment (ATICE) instrument. Reprinted with permission from de Jonghe et al (29).](image-url)
blood pressure decreases <90 mm Hg, one systolic blood pressure increase >200 mm Hg, three SpO2 decreases <80%, and one enteral feeding tube removal). There were no extubations and all adverse events were fully resolved by cessation of activity. This study clearly showed that an unconventional mobilization protocol could be performed in mechanically ventilated patients with success and safety.

Thomsen and colleagues expanded on the work by Bailey et al with another study from the LDS respiratory ICU (31). They sought to determine whether immobilization occurred unnecessarily in their other ICUs and was improved on transfer to the respiratory ICU with its focus on aggressive early ambulation. The primary end point of this study was ambulation and each patient served as his/her own control in this before-after cohort study. The investigators studied 104 patients. As seen in Figure 4, ambulation increased significantly after transfer to the respiratory ICU from another ICU. By multivariate logistic regression analysis, ambulation was predicted by transfer to the respiratory ICU (odds ratio 2.47; 95% confidence interval 1.9–3.4; \( p < .0001 \)), absence of sedatives (odds ratio 1.90; 95% confidence interval 1.2–3.2; \( p < .009 \)), female gender (odds ratio 1.88; 95% confidence interval 1.1–3.2; \( p < .019 \)) and lower Acute Physiology and Chronic Health Evaluation II score (odds ratio 1.06; 95% confidence interval 1.01–1.1; \( p < .017 \)). Eighty-eight percent of patients survived to hospital discharge with a median ambulation distance of 200 feet. This study also confirmed the important relationship between sedation and immobilization.

These two studies identified early mobilization as a feasible and safe intervention and set the stage for subsequent comparative interventional studies. It is important to note that the patients in these studies were cared for in another ICU for an average of 10 days before transfer to the respiratory ICU. At the time of these publications, whether even earlier therapy might be feasible and/or beneficial remained unknown.
Morris and colleagues reported the first prospective trial comparing early ICU mobilization with usual care (32). Mechanically ventilated adult patients were enrolled in the trial within 48 hrs of intubation. The assignment to mobilization protocol vs. usual care was done in a nonrandomized manner by block allocation in different ICUs. Patients in both groups were treated with protocols for sepsis resuscitation, glycemic control, daily sedative interruption, and ventilator liberation. The mobilization protocol involved a mobility team (critical care nurse, nursing assistant, physical therapist) using a progressive activity regimen (Fig. 5). The primary outcome of the study was the proportion of patients surviving to hospital discharge who received physical therapy. Secondary outcomes were days until the patient was first out of bed, number of ventilator days, ICU length of stay, and hospital length of stay among survivors.

A total of 330 patients were enrolled in the trial (n = 165 in each group). There were no adverse events, such as removal of medical devices noted during any of the mobilization sessions. Eighty percent of patients in the mobilization group had at least one physical therapy session compared with 47% in the usual care group (p < .001). The mobilization group had fewer days to first out of bed (8.5 vs. 13.7; p < .001) and fewer hospital days (14.9 vs. 17.2; p = .048).

The mobilization protocol in this study occurred only during time in the ICU. Whether ongoing aggressive mobilization after ICU discharge would have offered additional benefit is not known. Another limitation is the lack of blinding, leading to the potential for bias with regard to patient discharge disposition. The reason for shortened hospitalization is not known because the study did not report assessments of strength or functional condition. The authors concluded that further studies assessing these end points were merited.

Schweickert and colleagues recently reported findings from a prospective randomized trial of very early physical and occupational therapy from the inception of respiratory failure requiring mechanical ventilation (33). They evaluated medical ICU patients undergoing mechanical ventilation for <72 hrs who were functionally independent before ICU admission. The Barthel Index (34) was used to identify independent functional status, as this tool has demonstrated reliability when assessment is made by proxy (35). Patients randomized to the intervention group underwent a progressive therapy regimen focused on mobilization and achievement of occupational tasks (i.e., activities of daily living). Each morning, patients underwent sedative interruption (25). Once the patient was awake and able to follow commands, a physical and occupational therapist subjected patients to a sequential mobilization protocol. This protocol progressed from range of motion exercises to sitting at the edge of the bed, activities of daily living, transfer training, and ambulation. Progression of the mobilization protocol was dependent on patient tolerance and stability. Patients in the control group underwent physical therapy/occupational therapy as ordered by the primary care team typically occurring after extubation (16, 30, 31, 35–37). All functional outcomes were evaluated by therapists blinded to patient randomization assignment. The primary end point of the trial was the return to functional independence at hospital discharge. This was defined as the ability to perform activities of daily living (bathing, dressing, eating, grooming, transfer from bed to chair, toileting) and walk independently.

Intervention patients began therapy at 1.5 days after intubation compared with 7.3 days after intubation in the control group (p < .001), with several improved outcomes reported. Independent functional status at hospital discharge occurred in 59% of intervention patients compared with 35% of controls (p = .02). The intervention patients were noted to
CONCLUSIONS

Survivors of respiratory failure requiring mechanical ventilation are at high risk for neuromuscular weakness and functional impairment. These problems are often severe and persistent, and for many patients these difficulties may never fully resolve. Given the frequency with which immobilization occurs in these patients while in the ICU, it stands to reason to hypothesize that early mobilization may offer benefit. The area of early ICU mobilization is novel and there is limited evidence at present to guide clinicians. Nevertheless, recent studies have confirmed that mobilization of mechanically ventilated patients is feasible and safe. Furthermore, preliminary evidence suggests that such an intervention may offer improvement in outcomes for these high-risk patients. Further trials to investigate the potential benefits of ICU mobilization are warranted.

REFERENCES


Figure 5. Progressive activity regimen. ICU, intensive care unit; OOB, out of bed; ROM, range of motion. Reprinted with permission from Morris et al (32).

have greater unassisted ambulatory distance (110 vs. 0 feet; p = .004) and more ventilator-free days (23.5 vs. 21.1; p = .05). The duration of ICU delirium was shorter in the intervention group (2.0 vs. 4.0 days; p = .03) in spite of no differences in sedatives administered.

Similar to the other studies (30–32), feasibility of early mobilization was again demonstrated in this trial. With a regimen targeting very early mobilization, many patients achieved activity milestones during mechanical ventilation: sitting on the edge of the bed (78%); standing (51%); transfer to a chair (43%); ambulating ≥2 steps (25%); and ambulating >100 feet (6%).

Major adverse events were uncommon—one event in 498 encounters (zero extubations, falls, or systolic blood pressure changes <90 mm Hg or >200 mm Hg; one desaturation <80%) and cessation of therapy as a result of adverse events occurred rarely (4% of all sessions). This study differed from the previous studies in that mobilization occurred extremely early (~1.5 days after intubation) and measured functional outcomes in a randomized, blinded fashion.


