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Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial

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Summary

Background Long-term complications of critical illness include intensive care unit (ICU)-acquired weakness and neuropsychiatric disease. Immobilisation secondary to sedation might potentiate these problems. We assessed the efficacy of combining daily interruption of sedation with physical and occupational therapy on functional outcomes in patients receiving mechanical ventilation in intensive care.

Methods Sedated adults (≥18 years of age) in the ICU who had been on mechanical ventilation for less than 72 h, were expected to continue for at least 24 h, and who met criteria for baseline functional independence were eligible for enrolment in this randomised controlled trial at two university hospitals. We randomly assigned 104 patients by computer-generated, permuted block randomisation to early exercise and mobilisation (physical and occupational therapy) during periods of daily interruption of sedation (intervention; n=49) or to daily interruption of sedation with therapy as ordered by the primary care team (control; n=55). The primary endpoint—the number of patients returning to independent functional status at hospital discharge—was defined as the ability to perform six activities of daily living and the ability to walk independently. Therapists who undertook patient assessments were blinded to treatment assignment. Secondary endpoints included duration of delirium and ventilator-free days during the first 28 days of hospital stay. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00322010.

Findings All 104 patients were included in the analysis. Return to independent functional status at hospital discharge occurred in 29 (59%) patients in the intervention group compared with 19 (35%) patients in the control group (p=0·02; odds ratio 2·7 [95% CI 1·2–6·1]). Patients in the intervention group had shorter duration of delirium (median 2·0 days, IQR 0·0–6·0 *vs* 4·0 days, 2·0–8·0; p=0·02), and more ventilator-free days (23·5 days, 7·4–25·6 *vs* 21·1 days, 0·0–23·8; p=0·05) during the 28-day follow-up period than did controls. There was one serious adverse event in 498 therapy sessions (desaturation less than 80%). Discontinuation of therapy as a result of patient instability occurred in 19 (4%) of all sessions, most commonly for perceived patient-ventilator asynchrony.

Interpretation A strategy for whole-body rehabilitation—consisting of interruption of sedation and physical and occupational therapy in the earliest days of critical illness—was safe and well tolerated, and resulted in better functional outcomes at hospital discharge, a shorter duration of delirium, and more ventilator-free days compared with standard care.

Funding None.

Introduction

Advances in the management of mechanically ventilated patients have improved outcomes and survival rates for this patient population.[1–3] As patients survive acute illness, long-term complications are more apparent. Weakness is a frequent complication and is associated with major disability and protracted rehabilitation.[4–6] In addition to physical debility, neuropsychiatric dysfunction is often profound. Delirium during intensive care unit (ICU) stay (ICU-associated delirium) is common in patients undergoing mechanical ventilation, and is associated with increased mortality,[7] longer length of stay in intensive care and in hospital,[8] and increased duration of ventilation.[7]

Clinicians working in the ICU often focus on treating circulatory, respiratory, and renal function to ensure patient survival. Accordingly, most patients on mechanical ventilation receive sedative and analgesic drugs to reduce distress and oxygen consumption;[9] however, this approach can result in long periods of unconsciousness and immobility.[10] Protocols geared to keeping sedation to a minimum, such as daily interruption of sedation,[11] and mobilisation of mechanically ventilated patients via physical therapy[12,13] in the earliest days of critical care, can result in improved patient outcomes. Specifically, observational studies of patients on mechanical ventilation for at least 4 days who were subsequently transferred to a dedicated respiratory ICU (post-acute care) have shown that physical therapy is feasible, safe, and promotes more rapid return to ambulation.[12,13] More recently, in a prospective, non-randomised cohort study, Morris and colleagues[14] showed that an early mobilisation team increased physical therapy services for medical ICU patients with respiratory failure; this intervention also shortened length of stay in the ICU and in hospital.

Additionally, the identification of ICU-associated delirium and its association with poor outcomes has highlighted the need for interventions that might alter its course.[15] Although several possible factors might result in ICU-associated delirium, so far only sedation with dexmedetomidine as a replacement for a benzodiazepine has been shown to reduce the duration of ICU-associated delirium.[16]

The implementation of daily interruption of sedation combined with physical and occupational therapy in the earliest days of critical illness might prevent sedative-related immobility. We postulated that this intervention, tested in a randomised controlled trial, would affect both functional outcomes and neuropsychiatric outcomes, such as ICU-associated delirium.

Methods

Patients

We recruited study participants at two medical centres: University of Chicago Medical Center (Chicago, IL, USA) and University of Iowa Hospitals (Iowa City, IA, USA). The institutional review boards at both centres approved the study, and written informed consent was obtained from participants or their authorised representatives.

Patients in the medical ICU were screened daily to identify adults (≥18 years of age) who had been on mechanical ventilation for less than 72 h, were expected to continue for at least 24 h, and who met criteria for baseline functional independence (defined a priori as a Barthel Index score ≥70 obtained from a proxy describing patient function 2 weeks before admission).[17,18] Patients were excluded for the following reasons: rapidly developing neuromuscular disease, cardiopulmonary arrest, irreversible disorders with 6-month mortality estimated at more than 50%, raised intracranial pressure, absent limbs, or enrolment in another trial.

Procedures

Patients were randomly assigned in a 1:1 ratio to exercise and mobilisation (physical and occupational therapy) beginning on the day of enrolment (intervention) or to standard care with physical and occupational therapy delivered as ordered by the primary care team (control). Neither site routinely provides physical therapy for patients who are on mechanical ventilation for less than 2 weeks, nor has dedicated physiotherapists for such practice. At both sites, a computer-generated, permuted block randomisation scheme was used to allocate patients to study group. Each assignment was designated in a consecutively numbered, sealed, opaque envelope by an investigator with no further involvement in the trial.

Every morning, unresponsive patients in the intervention group underwent passive range of motion exercises for all limbs (ten repetitions in all cardinal directions). Sedatives were interrupted as previously described.[1] Therapy was delivered by a physical and occupational therapist and coordinated with daily interruption of sedation. Once patient interaction was achieved, sessions began with active assisted (with manual assistance) and active (independent) range of motion exercises in the supine position. If these exercises were tolerated, treatment was advanced to bed mobility activities, including transferring to upright sitting. Sitting balance activities were followed by participation in activities of daily living (ADLs) and exercises that encouraged increased independence with functional tasks. The session progressed to transfer training (ie, repetition of sit-to-stand transfers from bed to chair or bed to commode), and finally pre-gait exercises and walking. Progression of activities was dependent on patient tolerance and stability. Therapy intervention continued on a daily basis throughout the patient's hospital stay until he or she returned to a previous level of function or was discharged.

The following criteria indicated unstable patient conditions that prevented the initiation or continuation of physical and occupational therapy: mean arterial blood pressure less than 65 mm Hg or more than 110 mm Hg, or systolic blood pressure more than 200 mm Hg; heart

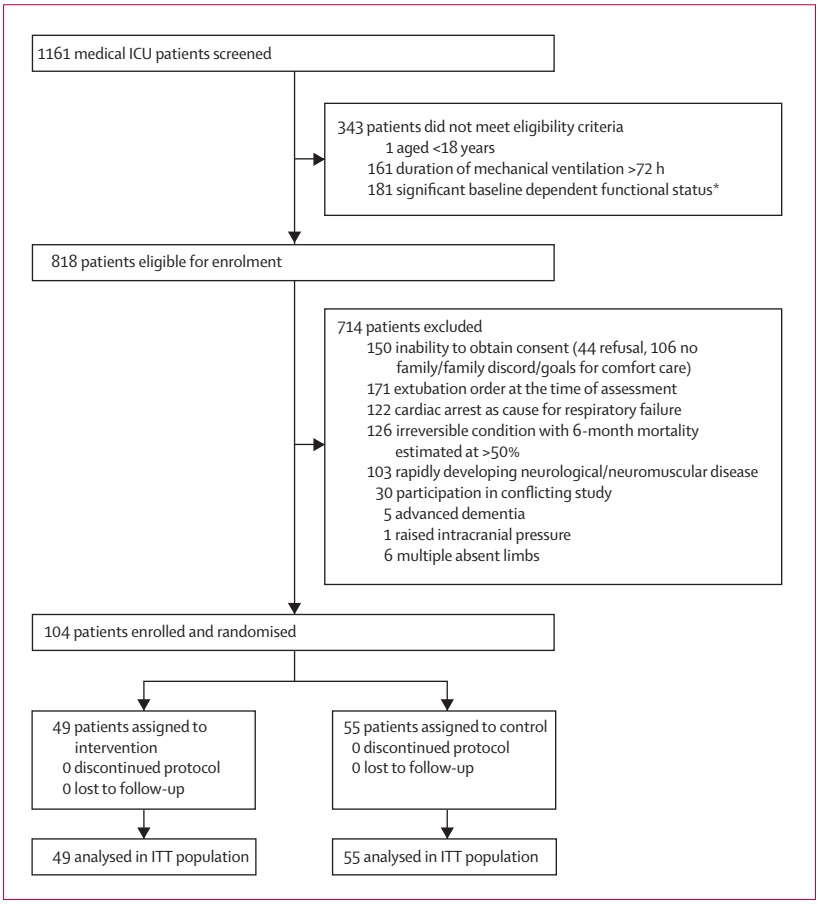

***Figure 1*: Trial profile**

ICU=intensive care unit. ITT=intention-to-treat. *Defined as a Barthel Index score describing health 2 weeks before admission of less than 70.

	Intervention (n=49)	Control (n=55)
Age (years)	57·7 (36·3–69·1)	54·4 (46·5–66·4)
Female	29 (59%)	23 (42%)
Black race	30 (61%)	31 (56%)
Barthel Index score	100 (85–100)	100 (90–100)
Body-mass index (kg/m²)	27·4 (25·1–32·4)	28·0 (23·5–34·1)
APACHE II score	20·0 (15·8–24·0)	19·0 (13·3–23·0)
Sepsis	42 (86%)	45 (82%)
Diabetes	18 (37%)	18 (33%)
Primary diagnosis on admission to intensive care		
Acute lung injury	27 (55%)	31 (56%)
COPD exacerbation	4 (8%)	6 (11%)
Acute exacerbation of asthma	5 (10%)	4 (7%)
Sepsis	7 (14%)	9 (16%)
Haemorrhage	1 (2%)	2 (4%)
Malignancy	2 (4%)	1 (2%)
Other	3 (6%)	2 (4%)

Data are number of patients (%) or median (IQR). APACHE II=Acute Physiology and Chronic Health Evaluation II. COPD=chronic obstructive pulmonary disease. Barthel Index scale 0–100, APACHE II scale 0–71.

Table 1: **Baseline characteristics of the study population**

rate less than 40 beats per min or more than 130 beats per min; respiratory rate less than 5 breaths per min or more than 40 breaths per min; and pulse oximetry less than 88%. Additionally, the following findings were contraindications for initiation of therapy: raised intracranial pressure; active gastrointestinal blood loss; active myocardial ischaemia; continuing procedures including intermittent haemodialysis (but not including continuous ultrafiltration or haemodialysis); patient agitation that needed increased sedative administration in the past 30 min; and unsecure airway. Further criteria that prevented continuation of therapy were marked ventilator asynchrony; patient distress (evidenced by non-verbal cues, gestures); the patient being physically combative; new arrhythmia; concern for myocardial ischaemia; and concern for airway device integrity.

Patients in both intervention and control groups were managed by goal-directed sedation guided by the Richmond Agitation Sedation Scale (RASS)[19,20] and underwent daily interruption of sedatives or narcotics, or both. Contraindications to daily interruption of sedation were: persisting neuromuscular blockade; sedative infusion for active seizures or alcohol withdrawal; escalating sedative doses because of persisting agitation; evidence of active myocardial ischaemia in the previous 24 h; and evidence of raised intracranial pressure. Study personnel undertook daily independent neurological assessments of patients by use of the RASS for level of arousal and the Confusion Assessment Method for the ICU for delirium and coma.[21,22]

Weaning patients from mechanical ventilation was done via a protocol,[3] with the decision to extubate made by the primary care team. All patients were started on enteral feeding and those who showed three glucose concentrations of more than 8·3 mmol/L were treated with insulin infusions.[23]

The primary endpoint was defined a priori as the number of patients returning to independent functional status at hospital discharge. Independent functional status was defined as the ability to perform six ADLs (bathing, dressing, eating, grooming, transferring from bed to chair, using the toilet)[24,25] and walking independently. Historically, functional assessments of survivors of critical illness include outcomes of ADLs and walk distance.[4,12,13,26,27] This composite endpoint was selected to reflect these milestones and the targeted goals of the intervention. The rating scale of the Functional Independence Measure was used to quantify functional status. ADL scores that were rated ≥5 were deemed as performed independently by the patient (ie, no need for physical assistance).[28]

Secondary endpoints were: (1) number of hospital days with delirium; (2) number of days alive and breathing without assistance (ventilator-free days) during the first 28 days of hospital stay; and (3) length of stay in the ICU and in hospital. Additionally, the following measurements were taken at hospital discharge: (1) Barthel Index score; (2) number of functionally independent ADLs; (3) distance walked without assistance; (4) number of patients diagnosed with ICU-acquired paresis;[29] and (5) hand-grip strength scoring at ICU and hospital discharge.

Patients were assessed by physical and occupational therapists who were unaware of randomisation assignment. Every 48 h, these therapists assessed patient strength and ability to perform ADLs and to walk, including a final assessment and Barthel Index scoring within 24 h of discharge. Strength in the upper and lower extremities was scored by use of the Medical Research Council (MRC) examination,[30,31] followed by three measurements of dominant hand dynamometry (Jamar hand-grip dynamometer; Sammons Preston Rolyan, Bolingbrook, IL, USA). ICU-acquired paresis was diagnosed when an awake and attentive patient had a muscle strength sum score of less than 48 when all muscle groups were able to be assessed.[29]

To maintain blinding, the group of assessment therapists was distinct from the therapists who undertook the intervention. Before each assessment, the patients and any visitors were instructed (via a structured introductory statement) not to discuss previous interventions. Furthermore, assessments occurred in the afternoon at a time distant from the morning therapy intervention.

Safety was monitored by research staff and bedside nurses continuously during the study. In accordance with the requirements of the institutional review boards, if research-related adverse events were to occur, the intervention should be stopped, followed by immediate medical treatment in the ICU. Furthermore, all serious

adverse events were to be reported to the institutional review boards within 48 h.

Therapy sessions in which the patient met the criteria for instability or in which unplanned extubation or equipment removal occurred were tracked prospectively. Individual decisions by the primary care team or intervention team to discontinue a therapy session were categorised and reported. Serious adverse events, in accordance with recently published literature, included fall to knees, endotracheal tube removal, systolic blood pressure more than 200 mm Hg, systolic blood pressure less than 90 mm Hg, and desaturation to less than 80%.[12] Finally, the time to taken to accomplish additional functional milestones (such as the first day getting out of bed, standing, marching in place, transferring to a chair, walking [even with assistance]) were recorded from nursing and physiotherapy notes to emphasise patient progression in the two groups.

Statistical analysis

On the basis of observations of functional outcomes in a cohort of critically ill patients with respiratory failure who were functional at admission to intensive care, we noted that 50% of patients achieved return of independent functional status at hospital discharge. We calculated that a total sample size of 100 patients would be needed to detect a 30% difference in the number of patients achieving return to independent functional status between the two groups with 80% power and a two-sided significance level of 0·05.

Data were analysed by an intention-to-treat approach. Patients who died during the study were assigned scores of 0 for ventilator-free days, strength testing (MRC examination and hand grip), ADL total, walk distance, and Barthel Index score. We used the χ^2 test or Fisher Exact test (as appropriate) to compare categorical variables between the two study groups, including the primary endpoint, and the Wilcoxon-Mann-Whitney two-sample rank-sum test or *t* tests to compare continuous variables.

To compare the effect of the treatment protocol on the time to return to independent functional status, we used time-to-event analysis. A cumulative event curve (censored endpoints) was estimated with the Kaplan-Meier procedure. The effect of the treatment protocol on the endpoint was compared between groups with the log-rank test. Additional analysis was done with logistic and Cox regression models that adjusted for the main baseline factors that predict outcomes (age, APACHE II, presence of sepsis) and the presence of the intervention. We checked the assumption of proportionality of hazard functions in our Cox regression model. Hazard ratios (HRs), together with 95% CIs, were estimated with these models. To assess for an interaction between study centre and treatment with respect to the primary endpoint, we included an interaction term in a proportional odds logistic regression model with return to independent function as the dependent variable.

We used GraphPad Prism software (version 5.0) for all statistical analyses apart from the Cox regression analysis, which was done with SPSS software (version 8.0). An independent biostatistician reanalysed the final dataset and verified all our results. Significant differences between groups or across time were reported at the alpha level of 0·05. All reported p values are two-sided. This trial is registered with ClinicalTrials.gov, number NCT00322010.

	Intervention (n=49)	Control (n=55)	p value
Daily interruption of sedation			
Days of sedation with DIS (%)*	100% (100–100)	100% (100–100)	0·56
Duration of DIS per patient (h per day)	2·7 (0·8–6·5)	3·3 (1·0–8·9)	0·35
Time on mechanical ventilation with DIS (%)†	14% (5–33)	20% (5–44)	0·36
Sedation and analgesia duration			
Sedation duration (days)	2·7 (1·5–5·5)	4·3 (2·5–6·8)	0·06
Time on sedation (%)‡	69% (27)	68% (27)	0·84
Opiate duration (days)	2·3 (1·3–4·3)	3·3 (1·7–6·1)	0·14
Time on opiate (%)‡	65% (42–89)	71% (32–86)	0·64
Coma (days)	0·0 (0·0–0·2)	1·0 (0·0–3·0)	0·12
ICU days with coma (%)	0% (0–15)	8% (0–27)	0·21
Drug details, sedative and analgesic agents			
Patients receiving propofol	48 (98%)	53 (96%)	1·0
Propofol dose (mg/h)	99 (46–136)	96 (53–141)	0·98
Patients receiving opiate	48 (98%)	54 (98%)	1·0
Morphine equivalents (mg/h)	2·6 (0·7–5·4)	3·1 (0·9–6·1)	0·83
Patients receiving benzodiazepine	39 (80%)	48 (87%)	0·43
Lorazepam equivalents (mg/h)	0·02 (0·0–0·3)	0·02 (0·0–0·2)	0·89
Patients receiving haloperidol	8 (16%)	9 (16%)	0·80
Haloperidol (mg per day)	0 (0·0–0·0)	0 (0·0–0·0)	1·0
Nutrition and glycaemic control			
Goal calories given while intubated (%)	37% (11–58)	34% (15–58)	0·99
Blood glucose, morning concentration (mmol/L)	7·3 (6·6–8·2)	7·2 (6·7–8·1)	0·83
Patients receiving insulin infusion (%)	40 (82%)	42 (76%)	0·68
Reasons for resumption of sedation following interruption§			
Sustained anxiety or agitation	69 (55%)	101 (57%)	0·78
Sustained pain	5 (4%)	5 (3%)	0·74
Oxygen saturation <88% for >5 min	2 (2%)	11 (6%)	0·08
Two or more signs of respiratory distress	50 (40%)	60 (34%)	0·36
Reasons for unsuccessful spontaneous breathing trial¶			
Respiratory rate <8 breaths per min for ≥5 min	3 (2%)	2 (2%)	0·68
Oxygen saturation <88% for ≥5 min	5 (4%)	3 (2%)	0·72
Acute cardiac dysrhythmia	0 (0%)	1 (1%)	0·49
Two or more signs of respiratory distress	127 (94%)	126 (95%)	0·82

Data are median (IQR), mean (SD), or n (%). DIS=daily interruption of sedation. ICU=intensive care unit. *Eligible days began 36 h following start of mechanical ventilation. †Total duration of sedative and analgesic interruption (h) divided by duration of mechanical ventilation (h). ‡Proportion of hours undergoing continuous sedative/opiate infusion versus total duration of mechanical ventilation (h). §Resumption of sedation following interruption occurred 126 and 177 times in the intervention and control groups, respectively. Patients may have had more than one event. ¶Unsuccessful spontaneous breathing trials occurred 135 and 132 times in the intervention and control groups, respectively. Patients may have had more than one event.

Table 2: **Therapy details and protocol adherence according to study group**

	Intervention (n=49)	Control (n=55)	p value
Return to independent functional status at hospital discharge	29 (59%)	19 (35%)	0·02
ICU delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–7·0)	0·03
Time in ICU with delirium (%)	33% (0–58)	57% (33–69)	0·02
Hospital delirium (days)	2·0 (0·0–6·0)	4·0 (2·0–8·0)	0·02
Hospital days with delirium (%)	28% (26)	41% (27)	0·01
Barthel Index score at hospital discharge	75 (7·5–95)	55 (0–85)	0·05
ICU-acquired paresis at hospital discharge	15 (31%)	27 (49%)	0·09
Ventilator-free days*	23·5 (7·4–25·6)	21·1 (0·0–23·8)	0·05
Duration of mechanical ventilation (days)	3·4 (2·3–7·3)	6·1 (4·0–9·6)	0·02
Duration of mechanical ventilation, survivors (days)	3·7 (2·3–7·7)	5·6 (3·4–8·4)	0·19
Duration of mechanical ventilation, non-survivors (days)	2·5 (2·4–5·5)	9·5 (5·9–14·1)	0·04
Length of stay in ICU (days)	5·9 (4·5–13·2)	7·9 (6·1–12·9)	0·08
Length of stay in hospital (days)	13·5 (8·0–23·1)	12·9 (8·9–19·8)	0·93
Hospital mortality	9 (18%)	14 (25%)	0·53

Data are n (%), median (IQR), or mean (SD). ICU=intensive care unit. *Ventilator-free days from study day 1 to day 28. Barthel Index scale 0–100, APACHE II scale 0–71.

Table 3: **Main outcomes according to study group**

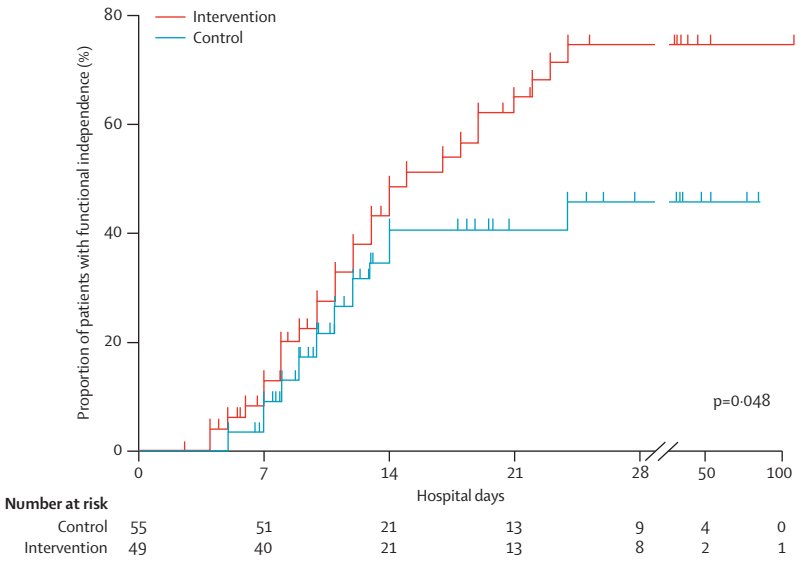

Figure 2: **Probability of return to independent functional status in intervention and control groups**

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From June, 2005, to October, 2007, 1161 patients were screened, of whom 104 were enrolled and randomised. Figure 1 shows the trial profile. Nine (18%) patients in the intervention group and 14 (25%) patients in the control group died before hospital discharge. All 104 patients were included in the intention-to-treat population. Table 1 shows the baseline characteristics of the enrolled patients.

Of the 49 patients in the intervention group, 46 (94%) underwent physical and occupational therapy (three died before any intervention). For the intervention patients as a group, therapy occurred on 87% of days on study. There are three reasons why therapy did not occur all of the time: (1) the patient was unstable (defined by criteria listed in the Methods section); (2) the patient was unavailable for therapy (competing procedure or travel for intervention or test outside of the ICU); and (3) goals of care were changed to comfort measures only.

The median duration of physical and occupational therapy during mechanical ventilation differed between groups (intervention 0·32 h per day, IQR 0·17–0·48; control 0·0 h per day, 0·0–0·0; p<0·0001). Patients in the intervention group underwent therapy at a median of 1·5 days (1·0–2·1) after intubation whereas controls had therapy initiated at 7·4 days (6·0–10·9) after intubation (p<0·0001). However, time to therapy for patients in the control group was shorter than the median length of stay in the ICU (7·9 days, 6·1–12·9). The median duration of physical and occupational therapy during the time not receiving mechanical ventilation was similar between groups (intervention 0·21 h per day, 0·08–0·33; control 0·19 h per day, 0·0–0·38; p=0·70). Of 22 patients in the control group who were extubated and survived to hospital discharge but never returned to independent functional status, 21 (95%) underwent therapy.

Sedation and analgesia practice did not differ between groups, including occurrence and duration of daily interruption of sedation and proportion of time on mechanical ventilation that was spent receiving sedative or opiate. However, total sedation duration was longer in controls than in patients in the intervention group, which reflects the difference in duration of mechanical ventilation between the groups (table 2). Reasons and occurrence rates for resumption of sedation were similar for both groups.[3] Both groups had very high spontaneous breathing trial performance rates on days when this screen was passed (intervention 200 [96%] of 209); control 197 [98%] of 201). Reasons and occurrence rates for unsuccessful spontaneous breathing trials were also similar between groups.[3] All 104 patients received enteral nutrition only, and both groups were similar with regard to goal calories given while intubated, median morning glucose concentration, and proportion of patients receiving insulin (table 2).

Return to independent functional status at hospital discharge occurred in more patients in the intervention group than in the control group (29 [59%] patients *vs* 19 [35%] patients; p=0·02; odds ratio 2·7 [95% CI 1·2–6·1]; table 3). A log-rank (survival) analysis for return to independent functional status confirmed this

observation (figure 2), and showed that the effect of the intervention is delayed by approximately 2 weeks. Variables associated with achievement of functional independence by Cox proportional hazards analysis were age (hazard ratio [HR] 0·96, 95% CI 0·94–0·98; p=0·001), absence of sepsis (HR 2·26, 1·03–4·97; p=0·04] and the intervention (HR 1·84, 1·02–3·31; p=0·04). No association was detected with APACHE II score (HR 0·97, 0·92–1·02; p=0·22). There was no significant interaction between study centre and treatment with regard to the primary endpoint (data not shown).

Patients in the intervention group had higher Barthel Index scores (table 3), a higher number of independent ADLs (table 4), and greater unassisted walking distance at hospital discharge than did controls (table 4). ICU-acquired paresis (MRC examination score <48) was noted at hospital discharge in 15 (31%) patients in the intervention group and in 27 (49%) controls (p=0·09). Figure 3 shows rates of independence with individual ADLs and walking. Median MRC examination score and hand-grip strength at hospital discharge did not differ between groups (table 4). Patients in the intervention group were able to achieve several activity milestones during mechanical ventilation, such as sitting at the side of the bed (38 patients [78%]), standing (25 patients [51%]), marching in place (13 patients [27%]), transferring to a chair (21 patients [43%]), walking two steps or more (12 patients [24%]), and walking more than 30·5 m (three patients [6%]).

The subsequent locations of patients after hospital discharge are shown in table 5. The median duration of ICU-associated delirium was half as long in patients in the intervention group than in controls despite no differences in sedation (table 3). Additionally, patients in the intervention group spent a median of 2·4 more days alive and breathing without ventilatory support (ventilator-free days). Length of stay in the ICU and in hospital did not differ between groups (table 3).

Serious adverse events were uncommon: one event in 498 physical and occupational therapy sessions (one desaturation less than 80%).[12] There were no extubations, falls, or systolic blood pressure changes less than 90 mm Hg or more than 200 mm Hg. Additionally, one radial arterial catheter was inadvertently removed in the intervention group. Discontinuation of therapy as a result of patient instability occurred in 19 (4%) of all sessions, most commonly for perceived patient-ventilator asynchrony.

	Intervention (n=49)	Control (n=55)	p value
Time from intubation to first PT/OT session (days)	1·5 (1·0–2·1)	7·4(6·0–10·9)	<0·0001
Independent ADLs total at ICU discharge	3 (0–5)	0 (0–5)	0·15
Independent ADLs total at hospital discharge	6 (0–6)	4 (0–6)	0·06
MRC examination score at hospital discharge	52 (25–58)	48 (0–58)	0·38
Hand-grip strength at hospital discharge (kg-force)	39 (10–58)	35 (0–57)	0·67
Greatest walking distance at hospital discharge (m)	33·4 (0–91·4)	0 (0–30·4)	0·004
Time from intubation to milestones achieved (days)			
Out of bed	1·7 (1·1–3·0)	6·6 (4·2–8·3)	<0·0001
Standing	3·2 (1·5–5·6)	6·0 (4·5–8·9)	<0·0001
Marching in place	3·3 (1·6–5·8)	6·2 (4·6–9·6)	<0·0001
Transferring to a chair	3·1 (1·8–4·5	6·2 (4·5–8·4)	<0·0001
Walking	3·8 (1·9–5·8)	7·3 (4·9–9·6)	<0·0001

Data are median (IQR). ADLs=activities of daily living. ICU=intensive care unit. MRC=Medical Research Council. PT/OT=physical therapy and occupational therapy. MRC examination scale 0–60.

Table 4: **Function and muscle strength outcomes according to study group**

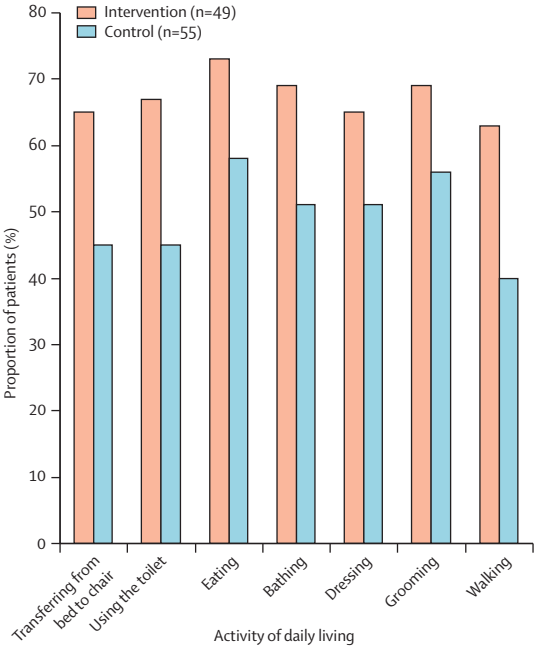

Figure 3: **Proportion of patients able to perform activities of daily living and to walk independently at hospital discharge**

Discussion

In this randomised controlled trial, daily interruption of sedation combined with physical and occupational therapy from the start of critical illness in patients on mechanical ventilation resulted in an improved return to (premorbid) independent functional status at hospital discharge compared with daily interruption of sedation and standard care. Additionally, patients in the intervention group had a shorter duration of ICU-associated delirium by 2·0 days and spent 2·4 more days alive and breathing without assistance than did controls. Early physical and occupational therapy, combined with daily interruption of sedation, was safe and well tolerated. Thus, this trial shows that both functional and psychological outcomes of patients on mechanical ventilation can be improved by the implementation of physical and occupational therapy in the earliest phases of critical illness. However, in this study, these outcomes did not translate into any difference in length of stay in

	Intervention (n=49)	Control (n=55)
Home*	21 (43%)	13 (24%)
Acute rehabilitation	13 (27%)	17 (31%)
Subacute rehabilitation	0 (0%)	6 (11%)
Long-term rehabilitation	5 (10%)	3 (5%)
Nursing home	1 (2%)	1 (2%)
Hospice	0 (0%)	1 (2%)
Death	9 (18%)	14 (25%)

*p=0·06 for comparison of home discharge to all other possible locations for the comparison of both groups.

Table 5: **Subsequent location of patients after hospital discharge**

the ICU or in hospital between intervention and control groups.

As critical illness incidence and survival increase, issues surrounding ICU recovery will affect many patients. Investigations have highlighted the substantial morbidity and mortality and increased health-care needs associated with ICU-acquired weakness and neuropsychiatric illness in survivors of critical illness.[4,32–34] Deep sedation and immobility might potentiate these complications, especially ICU-acquired weakness.[35] DeJonghe and colleagues[29] found that duration of mechanical ventilation before awakening to establish the diagnosis of ICU-acquired paresis was a risk factor for the presence of the condition, independent of the duration of multiple organ failure. Repeated daily passive mobilisation prevents muscle atrophy in mechanically ventilated patients receiving neuromuscular blocking agents.[36] Finally, studies have shown that keeping sedation to a minimum reduces the rate of ICU-related complications.[37,38]

The adverse effects of skeletal muscle immobility are well recognised; atrophic processes begin within 72 h and even healthy, well-nourished individuals can show loss in muscle mass and strength within 10 days of bed rest.[39,40] Furthermore, the loss of independence during acute hospital admission can be profound, even in the absence of critical illness.[41,42] Accordingly, mobilisation is prescribed to maximise return to independence and avoid complications of atelectasis, pressure wounds, indwelling catheters, and delirium.[43,44] However, mechanical ventilation and sedation displace these therapies from routine practice in the earliest days of critical illness. In this study, we implemented daily interruption of sedation combined with mobilisation done within 48 h of the start of critical care; this method is distinct from previous studies of mobilisation. This study shows the safety of this early intervention and quantifies clinical benefit.

Delirium and neuromuscular function are undoubtedly linked. Without intact cognition, physical activity is either self-limited or iatrogenically limited, cooperation with therapy is poor, and any immobilisation injury is likely to be exacerbated. Patients in post-acute care with persistent delirium have shown poor functional recovery.[45] In non-ICU inpatients, development of delirium during hospital admission is associated with a raised subsequent risk of cognitive impairment or dementia. The relation between the duration of ICU-associated delirium and chronic or permanent cognitive impairment is complex; limited data suggest such an association.[46] These functional and cognitive impairments might provide the most likely reason for the excess longer-term mortality associated with delirium.[7,47]

Sedative-induced immobility is a preventable contributor to ICU-acquired weakness and functional impairment. However, other factors exist, including systemic inflammation (particularly sepsis), age, drugs, and severity of illness. As shown in this study, sepsis and age were independently associated with functional dependence. Beyond simply reversing immobility, another factor might have contributed to the success of the intervention. Because there were substantial differences between functional measurements despite no significant difference in absolute MRC examination or hand-grip strength scores between groups, it is possible that patients had a learning effect. Indeed, learning to function independently despite weakness is a goal of physical and occupational therapy.

The nature of the intervention prevented any blinding from patient and health-care providers, and knowledge of group allocation and witnessed interventions risk bias of study results. To address this drawback, we randomly assigned patients to treatment groups and managed them with daily interruption of sedation, daily spontaneous breathing trials, strict glycaemic control, and balanced nutritional intake between groups during the course of mechanical ventilation. Most importantly, serial assessments were done in a manner to maintain blinding of the assessor. However, decisions about sedation initiation or reinitiation, extubation, and ICU and hospital discharge were not controlled by protocol and might have been affected by knowledge of the intervention. However, we noted no differences between groups in indication for sedation reinitiation and spontaneous breathing trial failure or performance rates. Furthermore, the post-ICU hospital admission duration reported for both groups in this study accord with findings from a cohort study of mobilisation.[14]

Rates and timing of physical and occupational therapy and nursing behaviours might have been additionally affected (in either direction) by other confounding factors. The data show that neither centre routinely performs physical and occupational therapy in patients who receive mechanical ventilation for less than 2 weeks without a developing neuromuscular disease. Although it is possible that other ICUs might practise more aggressive early physical or occupational therapy than our control group, we were able to find little evidence of such practice in the published literature.[48] Furthermore, recent studies highlight the infrequency of physical

therapy in the ICU.[14,49] For example, in a standard care group within a single-centre study directed at promoting the mobility of critically ill patients, only 47% of patients received physical therapy at any time during their hospital stay, and only 6% of patients received physical therapy at any time in the ICU.[14] In our study, patients in the control group for whom consultation of physical and occupational therapy would be typical (ie, extubated survivors unable to perform ADLs and unable to walk) received therapy 95% of the time. The median duration of therapy for patients not undergoing mechanical ventilation was similar between groups. These findings, together with a median time to therapy earlier than ICU discharge, suggest that the treatment given to the control group was a fair representation of routine care, and identify the very early ICU therapy as the difference between groups. The work by our group and by others[12–14] supports the feasibility and safety of early mobilisation in patients on mechanical ventilation in intensive care. Our study shows the benefits of this intervention on restoration of functional independence as well as delirium reduction. The trend towards better discharge rates to home (intervention 43% *vs* control 24%; p=0·06 for comparison of home discharge to all other possible locations for the comparison of both groups) is intriguing. We now need to determine whether early mobilisation in intensive care can enhance successful home discharge and reduce the burden of post-ICU rehabilitative care.

The results of this study cannot be assumed to be directly applicable to all patients on mechanical ventilation. This is a select population of patients—critically ill, yet independent in premorbid health. Trial enrolment rates reflect the selective nature of these patients, yet their baseline functional independence was necessary to prove the prevention of functional loss. Physical and occupational therapy probably cannot result in a functional status after critical illness that surpasses baseline health. The relation of improved functional status at hospital discharge with long-term outcomes in this population is unclear. Studies in patients with chronic obstructive lung disease, patients with traumatic brain injury, and in elderly hospital inpatients suggest connections with improved morbidity, quality of life, and survival.[41,50–53]

Thus, a strategy for whole-body rehabilitation—accomplished by interruption of sedation, protocol-driven spontaneous breathing trials, and physical and occupational therapy—resulted in better outcomes compared with current standard approaches to sedation and activity during mechanical ventilation and its recovery. Patients assigned to intervention had shorter duration of delirium and left the hospital with better functional status. This study highlights the robust outcomes that can be achieved with the coordinated efforts of multiple disciplines dedicated to the survival and mental and physical recovery of critically ill patients receiving mechanical ventilation.

Contributors

WDS, ASP, CN, JBH, and JPK participated in the conception of the trial. WDS, ASP, CN, AJP, CLE, LS, MM, MF, DD, JBH, and JPK participated in study design. WDS, MCP, ASP, CN, GAS, AB, KEM, and JPK recruited patients and collected data; AJP, CLE, LS, MM, MF, DD, and RB collected data alone. WDS, MCP, ASP, GAS, KEM, JBH, and JPK analysed the data. All authors participated in interpretation of the results. WDS drafted the manuscript, and all authors contributed to critical review and revision of the manuscript. All authors have seen and approved the final version of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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