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Functional electrical stimulation with cycling in the critically ill: A pilot case-matched control study

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MANUSCRIPT

TITLE: Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study

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ABSTRACT

**Purpose:** To determine (a) safety and feasibility of functional electrical stimulation (FES)-cycling and (b) compare FES-cycling to case-matched controls in functional recovery and delirium outcomes.

**Materials and Methods:** Sixteen adult ICU patients with sepsis ventilated for more than 48 hours and in ICU for at least four days. Eight subjects underwent FES-cycling in addition to usual care and were compared to eight case-matched control individuals. Primary outcomes were: safety and feasibility of FES cycling. Secondary outcomes were: physical function in intensive care test-scored on awakening (PFIT-s); time to reach functional milestones and incidence and duration of delirium.

**Results:** One minor adverse event was recorded. Sixty-nine out of total possible 95 FES sessions (73%) were completed. A visible or palpable contraction was present 80% of the time. There was an improvement in PFIT-s of 3.9/10 points in the intervention cohort with faster recovery of functional milestones. There was also a shorter duration of delirium in the intervention cohort.

**Conclusions:** The delivery of FES cycling is both safe and feasible. The preliminary findings suggest that FES-cycling may improve function and reduce delirium. Further research is required to confirm the findings of this study and evaluate the efficacy of FES-cycling.

**Keywords:** intensive care; rehabilitation; recovery of function; electric stimulation therapy; muscle weakness
INTRODUCTION

The initial insult of a critical illness has lingering repercussions for patients admitted to the intensive care unit (ICU) resulting in skeletal muscle wasting and weakness. This is particularly so for individuals with sepsis who experience high rates of intensive care acquired weakness (ICU-AW) [1] and prolonged diminution of their physical capabilities and cognitive functioning [2, 3]. Importantly an improvement in survival rates and increasing awareness of post intensive care syndrome [4] has resulted in a paradigm shift from mortality-based outcomes to include patient centered outcomes around activity limitation, disability, participation and quality of life [5].

Early mobility is shown to lead to improvements in physical function and delirium [6-9]. However, there is often a delay in commencement of therapy due to the inability of patients to participate as a result of sedation or delirium. There is increased interest in the use of assistive technology to aid early rehabilitation, without the need for volitional patient engagement [10]. A recent systematic review evaluating electrical muscle stimulation (EMS) in critically ill patients concluded that the outcomes of using EMS in this cohort were inconclusive due to the heterogeneity of the studies and outcome measures but that EMS may have a beneficial role in the ICU [11]. The studies to date have examined EMS in non-functional resting positions using isolated muscle groups, such as the quadriceps muscles [12-14]. Functional electrical stimulation (FES) is different to EMS as it recruits several muscles concurrently in functional patterns that mimic voluntary muscle activation. Use of FES-cycling compared with EMS enables cyclical muscle contraction of large lower limb muscle groups including quadriceps, hamstrings, gluteals and calf muscles. It is hypothesized that coordinated muscle contraction increases the muscle workload facilitating increased training of strength and force while minimizing muscle fatigue [15]. Electrical stimulation using FES-
cycling can translate to improvements in other functional tasks such as walking in other patient populations [16].

This is the first study to investigate the use of FES-cycling in critically ill patients. The primary aims of this study were to determine the safety and feasibility of FES-cycling; secondary aims were to assess its effects on physical function, ICU length of stay, and delirium compared to a matched-case control cohort.

MATERIALS AND METHODS

Study Design: This was a single center interventional observational study of critically ill patients with case-matched control comparisons at a quaternary ICU in Melbourne, Australia. Individuals were recruited into the intervention (FES-cycling) over a four-month period (January, March, May-June, July-August 2012). Institutional ethical approval was obtained for the pilot evaluation of FES-cycling. Written informed consent was obtained from the patient’s proxy in the first instance followed by continuation of consent from the patient once they were able to provide consent. Retrospective case-matching to identify control comparisons took place between January-December 2012. The institutional ethics committee approved a waiver of consent for case-matched controls.

Screening and Eligibility: Subjects were initially included if they were adults at least 18 years of age; admitted with a diagnosis of sepsis or severe sepsis as defined by American College of Chest Physicians Consensus Conference Guidelines [17]; were predicted, by the senior ICU physician on admission, to be mechanically ventilated (MV) for more than 48 hours and remain in the ICU for at least four days. The senior ICU physician made their prediction independent from the research team. Additionally those screened to have the
intervention were excluded if there were physical reasons for the intervention not to be applied such as the presence of an external fixator, pacemaker or defibrillator, open wound or skin abrasions; obesity, BMI > 40 (weight too high for cycle machine), or the treating senior intensive care physician deemed the patient to be approaching imminent death.

A control was identified for each of the eight subjects who underwent the interventional program (FES cycling). Matching was performed according to three a priori identified matching criteria. The order of matching priority and sub-categories for matching were: (1) Acute Physiology and Chronic Health Evaluation (APACHE II Score) – four categories (a: < 18 mild; b: 18-22 moderate; c: 23-27 severe; d: ≥ 28 very severe; (2) MV hours – three categories (a: < 72 hours; b: 72 hours-7 days; and c: > 7 days); and (3) age ± 15 years. If more than one matched participant was identified the matched case control was randomly selected using computer-generated random numbers. Severity of illness, mechanical ventilation time and age have been associated with increased risk of ICU-AW, and thus to minimize confounding individuals were matched on these three criteria.

**Study Procedures:**

*Protocols of care:*

Patients were managed in the unit according to institutional protocols for resuscitation and sepsis management including antibiotic treatment, sedation, delirium and nutritional support. All care was under the direct supervision of senior intensive care physicians and critical care qualified nursing staff with a nurse to patient ratio of one to one.

*Usual Care:* Physiotherapists routinely screened daily for awakening and presence of delirium using De Jonghe five-point criteria (awake defined as score of greater than three out of five)
and cognitive assessment method for ICU (CAM-ICU) respectively. Once awake, patients commenced rehabilitation involving early mobility activities such as sitting on the edge of bed, sitting out of bed, standing, marching in place and walking (if able) for up to a maximum of 15 minutes in duration per day.

**Intervention:** In addition to the usual care described above, eight subjects received FES-cycling, which aimed to commence within 96 hours of admission and continue daily until ICU discharge. The FES-cycling intervention involved a supine motorized cycle ergometer attached to a current controlled stimulator (RT-300 supine model and SAGE stimulator, Restorative Therapies, Ltd, Baltimore, Maryland, USA) (Figure 1).

Disposable adhesive gel electrodes were placed over the major muscles of the lower limb bilaterally including: quadriceps, hamstrings, gluteals and calf muscles. The FES-cycling was conducted for a minimum of 20 to a maximum of 60 minutes daily five times a week. Muscles were stimulated at specific stages throughout the cycling phase based on normal muscular activation patterns regulated by the bicycle software. FES-cycling continued until ICU discharge.

**Stimulation parameters:** Stimulation involved an alternating monophasic rectangular waveform current. The stimulation was applied at intensities to cause visible contraction in all muscle groups. The presence of a muscle contraction was specifically monitored in the quadriceps muscle using a four-point scoring system developed for the purpose of this study: (i) visible; (ii) palpable; (iii) flickers; and (iv) no contraction observed, and were assessed at five minute intervals if difficult to establish the presence of contraction.
Other stimulation parameters were pre-determined including: pulse duration: 300-400 μsecs and frequency: 30-50 Hz, with intensity increased to a maximum milli-amplitude of 140 mA [20]. Once the patient was awake and able to participate, they were provided with standardized encouragement to participate in training and workload resistance was increased incrementally [21].

**Outcome Measures:**

*Feasibility and Safety:* To determine the feasibility of the FES-cycling intervention, we examined: (i) length of time from ICU admission to first training session; (2) total number of sessions conducted during the intervention period; (3) percentage of total potential sessions completed and reasons not completed; and (4) number of sessions where muscle contractions were observed. The authors, in conjunction with senior intensive care physicians in the ICU developed criteria to determine when exercise training was unsafe to commence or should be ceased (see Box 1).

In a subgroup of patients receiving the intervention (n=5) the safety of FES cycling was examined by recording the variability in cardiovascular and respiratory bedside parameters. Major and minor adverse events were decided *a priori* and are outlined in the online supplementary Table E1. Patients were continuously monitored throughout the intervention session and 30 minutes after by the intervention physiotherapist and bedside critical care nurses. Pain levels were also monitored using a behavioral pain score whilst intubated and then a visual analogue scale to quantify any discomfort once the patient was able to communicate.
Trends in outcomes between FES-cycling and control cohort

In our center the physical function intensive care test score (PFIT-s) is routinely assessed on awakening. The PFIT-s is scored out of 10, with the minimum clinically important difference (MCID) previously established by Denehy and colleagues as > 1.5 points [22]. Patient performance on initial PFIT-s has been shown to be predictive of ICU length of stay and morbidity [22]. The treating physiotherapist also recorded the subject’s highest level of function on a daily basis using an 11-point hierarchical scoring system [23]. The time to reach a priori defined functional milestones (i.e., standing, first ambulation) and highest functional level was recorded at three time-points: (i) awakening, (ii) intensive care and (iii) acute hospital discharge. Delirium was assessed using the CAM-ICU tool at the time of physiotherapy assessments by routine care physiotherapists and extracted from the medical records for this study. Physiotherapists assessing physical function and delirium were unaware of the study being conducted.

Baseline demographics included age, gender, admission diagnosis and severity of illness scoring. Additionally number of sedation days and use of glucocorticoids was recorded. Intensive care length of stay (LOS), MV hours, tracheostomy requirement, acute hospital LOS, discharge destination and mortality were recorded.

Statistical analyses:
Descriptive statistics were reported as mean (standard deviation) or median (interquartile range) for parametric and non-parametric data respectively. Matched statistical analysis was performed using paired-t test or non-parametric equivalent for continuous data with mean difference and 95% confidence intervals calculated and Fisher’s exact statistical analyses for categorical variables were used. The level of statistical significance was set at alpha of 0.05.
Box-plot graphical analyses for differences in awakening PFIT-s were plotted between groups. All data were analyzed using SPSS for MacIntosh statistical software package (SPSS Inc, Version 21 Chicago, IL).

RESULTS
Seventy individuals were ventilated for more than 48 hours with a diagnosis of sepsis and expected to remain in the unit for at least four days over a four-month recruitment timeframe (January, March, May-June, July-August 2012). The control cohort was selected from a pool of 55 participants who were admitted to the ICU over the same period of time as the intervention cohort (Figure 2). Within the case-matching process no individuals who declined participation in the intervention were included. All participants in the intervention group were matched using the preset criteria from this pool.

Demographic data for patients in both groups is shown in Table 1. There were no significant differences in any of the matched variables. There were no significant differences between groups in terms of premorbid function (Table 1). Individuals included in this study were independent and high functioning in the community prior to admission with a small number of co-morbidities (Table 1). The mean (SD) time to awakening and commencement of usual care rehabilitation was comparable between groups (control 11.1 (5.9) versus intervention: 10.3 (8.1) days, p=0.685) (Table 1). Sedation duration and average daily propofol dosages were also comparable across both groups (Table 2).

Feasibility and Safety of FES-cycling
Seventy patients were screened and eight patients were recruited (11.5%). Time from recruitment to first intervention session was median (interquartile range): 15.3 (12.0-31.5)
hours. The mean (SD) number of cycling sessions conducted was 8.6 (2.5) during the intervention period, with a total of 69 sessions out of a possible 95 sessions (73%) provided.

The reasons for the remaining sessions not being delivered are given in Table 3.

No major adverse events were recorded. One minor adverse event occurred in the thirty minutes post-training period, whereby one subject had a transient desaturation to 86% for greater than one minute, requiring a temporary increase in fraction of inspired oxygen (FiO₂) from 0.4 to 0.6 for one hour.

The trends for cardiovascular and respiratory parameters are shown within each training session and for each of the five participants in Figure E1. The greatest difference between minimum and maximum values recorded were observed with heart rate with a variation of 20-40 beats per minute (Figure E1). Although there was a variation during the exercise session for respiratory rate and heart rate as shown by maximum to minimum variation, the values recorded at the start (5 minutes prior to commencing exercise) and 30 minutes post exercise training were similar for these parameters (Figure E1, Table E2).

The mean (SD) FES-cycling session time was 35.8±10.7 minutes, with mean±SD quadriceps intensity of 67.0±29.6 mA. A visible quadriceps muscle contraction was observed in 49 out of 69 sessions (71%); a palpable but not visible contraction was present in another 6 out of 69 sessions (9%).

*Trends in outcomes between FES-cycling and case-matched control cohort*

At awakening there was a clinically significant difference between groups for PFIT-scores compared with the reported MCID [22] and a trend toward statistical significance (p=0.060) (Table 4, Figure E2). There was a trend towards earlier and faster recovery of functional
milestones in the intervention group, which may have contributed to earlier discharge (Table 4). Fewer individuals required inpatient rehabilitation in the intervention group (n=3/7, 43%) compared to the control group (n=6/7, 86%), p=0.5. There was a lower frequency of delirium in the intervention versus control (25:87%) although this was not significant. Duration of delirium was significantly shortened in the intervention group (intervention: median 0.0 (0.0-3.0) days versus control: median 6.0 (3.3-13.3) days, p=0.042).

DISCUSSION

This is the first study to examine the safety and feasibility of FES-cycling in critically ill patients with sepsis. Based on our findings FES-cycling is safe and feasible as a therapeutic intervention. FES-cycling showed promising trends for functional outcomes. This study is non-randomised and involves a small sample size therefore inferences on efficacy are limited.

Safety limitations such as presence of a pacemaker or the weight limit of the cycle affected recruitment to the FES-cycling intervention (Figure 2). This is important to take into consideration when considering the feasibility of this intervention.

Despite liberal safety criteria for exercise training compared to previous criteria utilized in rehabilitation studies in the ICU setting [24], there were no serious adverse events and only one minor transient event (desaturation). Bedside monitoring of cardiorespiratory parameters also demonstrated that individuals with marginalized cardiac and respiratory reserve were still able to be exercised in-bed. Several participants were exercised during periods of marginal physiological reserve as indicated by high SOFA scores, high noradrenaline requirements, and respiratory support without deterioration in physiological signs. However,
given this study involved a small sample size; future studies should continue close monitoring of subjects whilst undertaking this form of exercise training in the ICU.

The application of FES-cycling was feasible, with >70% of possible sessions completed in the majority of subjects and a visible or palpable contraction present in 80% of subjects which is similar to a previous study involving EMS in septic critically ill participants that reported a perceptible contraction 77% of time [25]. Our study was similar with regards to stimulation parameters (frequency, pulse duration) and treatment duration to previous studies examining EMS in the critically ill, [20]. The inability to elicit a contraction on 20% of occasions in this study was consistent with previous research [25, 26]. This may be explained by increased tissue impedance related to edema and/or changes in muscle membrane excitability [14, 27, 28]. Further, factors such as gender, age and severity of edema have been related to increased difficulty of obtaining an adequate quadriceps contraction [26]. If obtaining a visible or palpable contraction is found to be an important factor influencing efficacy, other outcomes need to be explored that can sensitively and accurately quantify muscle contraction such as ultrasonography.

Another important consideration in terms of feasibility is the time to set up equipment and staffing required. The set up of FES-cycling can take up to 15 minutes in a routine patient and up to 30 minutes in a patient in whom a visible or palpable contraction is difficult or unable to be elucidated. The therapy can be delivered by one trained FES-cycling therapist in conjunction with assistance from the bedside nurse. This is often less staffing than might be required to initially mobilize and rehabilitate patients on awakening, which can take two or more therapists.
There is growing evidence to suggest that timing of rehabilitation may be important to achieve the greatest gains in functional recovery. Muscle wasting has been shown to occur early and rapidly with significant reductions in rectus femoris CSA observed within the first 10 days [29]. In our study FES-cycling was commenced at a median of 15.3 hours from recruitment. This is similar to Schweickert et al [7], who provided early conventional rehabilitation within a median of 1.5 days, despite the different inclusion criteria and patient demographics. Both studies examined individuals who were moderately unwell, however our study specifically examined individuals with sepsis. Our findings are promising and in line with Schweickert [7] demonstrating trends toward improvement in functional independence and shorter delirium duration in individuals receiving early rehabilitation.

Consistent trends toward improvement were observed in the functional milestones in the intervention group resulting in higher levels of function on awakening and earlier return to functional independence in this group compared with the controls. Given the positive and consistent direction of findings in functional outcomes, we believe the FES-cycling provides a promising early intervention in the critically ill.

Limitations and Future Directions

The major limitation of this study is the small sample size and case-control design. The study was not designed to be powered to detect a meaningful difference between groups. Therefore it is important to caution readers as to the statistical findings and ability to draw meaningful comparisons between the two groups in terms of functional outcomes and frequency and duration of delirium. However the trends in results were all in a positive direction and thus promising. To minimize bias, selection and assessment occurred independent of the research team and both groups were comparable in terms of baseline demographics including
premorbid functioning and comorbidities (which were not matched). A further limitation for using FES-cycling is that the inclusion criteria are restrictive which impacts screening: recruitment ratios.

Further research is needed to determine the efficacy of FES-cycling in the critically ill population including longer-term effects of this treatment on function, delirium and cognitive function in larger patient cohorts.

CONCLUSIONS:
In conclusion, this study demonstrated that FES-cycling in a moderately unwell septic cohort was safe and feasible. It also suggests that FES-cycling may facilitate earlier and faster functional recovery and reduce the incidence and duration of delirium.

Acknowledgements: We would like to thank Dr Steven Van der Hoorn for statistical assistance, and Catherine Granger and Joleen Rose for assistance with delivering the intervention training sessions.

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Council R.D. Wright Biomedical Fellow. None of the funding bodies, fellowships or equipment companies was involved or influenced the design or publication of this study.

Figures and Tables Legends:

Box 1: Safety guidelines for exercise [21]
Abbreviations: cmH₂O, centimeters of water; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; HR, heart rate; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; min, minute; PEEP, positive end expiratory pressure; RR, respiratory rate; s, seconds; spO₂, saturation of peripheral oxygen; ug, micrograms.

Figure 1: FES-cycling machine (RT-300 supine model and SAGE stimulator, Restorative Therapies, Ltd, Baltimore, Maryland, USA).

Figure 2: Flow of participants diagram
Abbreviations: n, number; PMM, premorbid mobility; SCI, spinal cord injury.

Table 1: Baseline demographics of cohort
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II Score, comm. Of trad rehab, commencement of traditional rehabilitation; MV, mechanical ventilation; n, number; SD, standard deviation; %, percentage.

Table 2: Sedation, delirium and general outcomes comparing intervention and case-matched controls.
Abbreviations: DC dest, discharge destination; GC, glucocorticoids; ICU, intensive care unit; LOS, length of stay; mg/hr, milligrams per hour; n, number; SD, standard deviation; ug/hr, micrograms per hour; %, percentage.

Table 3: Reasons for non-commencement of exercise sessions in the intervention cohort
Abbreviations: n, number; FiO₂, fraction of inspired oxygen.
Table 4: Comparison between intervention and controls for time to reach functional milestones and awakening PFIT-scores

Abbreviations: amb, ambulation; a-PFIT-s, awakening Physical Function intensive care test score; indep amb, independent ambulation; mean diff, mean difference; MCID, minimally important clinical difference; SD, standard deviation; SOEOB, sitting on the edge of the bed; 95% CI, 95% confidence interval.
References:


**INTERVENTION ARM**

Patients meeting the inclusion criteria (n=70)

Patients excluded from intervention arm (n=62)
- Ineligible:
  - Primary neurological insult n=1
  - Spinal cord injury n=1
  - Poor PMM n=5
  - Imminent death n=5
  - Pacemaker n=7
  - Poor skin integrity or orthopedic restriction to using FES-cycling equipment n=11
  - Obesity n=4
  - Other new neurological or orthopaedic impairment affecting function n=12

Eligible but not recruited:
- Family declined n=7
- Unable to consent in timeframe n=9

Intervention arm (n=8)

**CONTROL ARM**

Patients meeting the inclusion criteria (n=70)

Patients excluded from case matching arm (n=15)
- Ineligible:
  - Primary neurological insult n=1
  - Spinal cord injury n=1
  - Poor PMM n=5

Eligible but not included:
- Patients in intervention cohort n=0

n=55 available for case-matching

Control arm (n=8)

**Figure 1: Flow of participants diagram**

Abbreviations: n, number; PMM, premorbid mobility; SCI, spinal cord injury.

Fig. 2
Table 1: Baseline demographics of cohort

Data is represented as mean±SD or n, % unless specifically stated in the table

<table>
<thead>
<tr>
<th></th>
<th>Control mean±SD (n=8)</th>
<th>Intervention mean±SD (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60.5±18.6</td>
<td>62.5±17.7</td>
</tr>
<tr>
<td>Gender male n (%)</td>
<td>4 (50%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Independent ambulation (no gait aid) (n, %)</td>
<td>8 (100%)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>19.6 (4.5)</td>
<td>25.0 (4.3)</td>
</tr>
<tr>
<td>Functional Comorbidity Index (30) (median [IQR])</td>
<td>3.0 [0.5-4.7]</td>
<td>2.5 [0.2-6]</td>
</tr>
<tr>
<td>MV, hours median [IQR]</td>
<td>190.0 (55.4-427.5)</td>
<td>197.8 (81.6-628.6)</td>
</tr>
<tr>
<td>Tracheostomy inserted n (%)</td>
<td>3 (37%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Time to awakening and commencement of conventional rehab, days</td>
<td>11.1±5.9</td>
<td>10.3±8.1</td>
</tr>
</tbody>
</table>

Source of sepsis n (%)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=8)</th>
<th>Intervention (n=8)</th>
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</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>5 (62%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>2 (25%)</td>
<td>3 (37%)</td>
</tr>
<tr>
<td>Urological</td>
<td>0 (0%)</td>
<td>1 (12%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>1 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>20.3±7.5</td>
<td>20.3±7.9</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II Score, BMI, body mass index; MV, mechanical ventilation; n, number; SD, standard deviation; %, percentage.
Table 2: Sedation, delirium and general outcomes comparing intervention and controls.

Data represented as median (25th-75th IQR) unless specifically stated otherwise in table.

<table>
<thead>
<tr>
<th></th>
<th>Control median (IQR) (n=8)</th>
<th>Intervention median (IQR) (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sedation and other medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of sedation, days</td>
<td>7.0 (4.5-10.5)</td>
<td>5.0 (3.3-15.0)</td>
</tr>
<tr>
<td>Average daily propofol dose (mg/hr)</td>
<td>95.5 (54.8-133.2)</td>
<td>81.4 (68.5-156.6)</td>
</tr>
<tr>
<td>GC n (%)</td>
<td>3 (37%)</td>
<td>5 (62%)</td>
</tr>
<tr>
<td>Duration of GC, days</td>
<td>10 (8-11)</td>
<td>5 (4-12.5)</td>
</tr>
<tr>
<td>Highest level of vasopressor (noradrenaline) support on day 1, ug/hr in mean±SD</td>
<td>12.3±7.6</td>
<td>24.5±20.3</td>
</tr>
<tr>
<td><strong>Delirium</strong></td>
<td></td>
<td></td>
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<tr>
<td>Delirium incidence n (%)</td>
<td>7 (87%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Duration of delirium, days</td>
<td>6.0 (3.3-13.3)</td>
<td>0.0 (0.0-3.0)</td>
</tr>
<tr>
<td><strong>Discharge destination and length of stay</strong></td>
<td></td>
<td></td>
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<tr>
<td>DC Dest†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehab</td>
<td>6 (86%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Home</td>
<td>1 (14%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Mortality n (%)</td>
<td>1 (12%)</td>
<td>1 (12%)</td>
</tr>
<tr>
<td>ICU LOS, days</td>
<td>13.5 (10.5-31.0)</td>
<td>12.0 (5.5-21.5)</td>
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<tr>
<td>Hospital LOS, days</td>
<td>31.0 (21.5-62.3)</td>
<td>24.0 (19.5-40.8)</td>
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</tbody>
</table>

Abbreviations: DC dest, discharge destination; GC, glucocorticoids; ICU, intensive care unit; LOS, length of stay; mg/hr, milligrams per hour; n, number; SD, standard deviation; ug/hr, micrograms per hour; %, percentage.

†Duration of GC, days is reported only for those who received any glucocorticoids during their hospital stay

b p-value calculated on matched pairs to determine presence of statistical significance between groups (p=0.042)

c reported on n=7 in each arm secondary to n=2 deceased across two groups
Table 3: Reasons for non-commencement of exercise sessions in the intervention cohort

<table>
<thead>
<tr>
<th>Subject</th>
<th>Actual sessions commenced/out of total possible (%)</th>
<th>Reasons for non commencement</th>
<th>Number of sessions not conducted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/35 (65.7%)</td>
<td>Surgical or investigational medical procedure</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High RR &gt; 35 breaths/minute</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Febrile and heart rhythm irregularities</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Actively bleeding and worsening sepsis leading to death</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>9/16 (56.3%)</td>
<td>Febrile and heart rhythm irregularities</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High RR &gt; 35 breaths/minute</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigational medical procedure</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>5/5 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3/4 (75%)</td>
<td>Severe agitation</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>4/4 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10/12 (83.3%)</td>
<td>Heart rhythm irregularities</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient declined</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>13/17 (76.5%)</td>
<td>High FiO₂ (1.0) and inotropic support (40 ug of noradrenaline/min)*</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart rhythm irregularities</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigational medical procedure</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>2/2 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** n, number; FiO₂, fraction of inspired oxygen.

* Safety criterion for exercise set at < 0.6 FiO₂ and inotropic support < 30 ug of noradrenaline/min – above the safety criterion for commencement of exercise.
Table 4: Comparison between intervention and controls for time to reach functional milestones and awakening PFIT-scores

<table>
<thead>
<tr>
<th>Functional activity</th>
<th>Control mean (SD)</th>
<th>Intervention mean (SD)</th>
<th>Mean diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-PFITs</td>
<td>2.9±1.8</td>
<td>5.3±1.9</td>
<td>**3.9 (-2.8-10.6)</td>
</tr>
<tr>
<td>Time to stand, days</td>
<td>14.6±6.3</td>
<td>10.75±8.8</td>
<td>-3.9 (-10.6-2.8)</td>
</tr>
<tr>
<td>Time to marching in place, days</td>
<td>16.0±7.8</td>
<td>12.28±11.6</td>
<td>*-3.7 (-14.4-7.0)</td>
</tr>
<tr>
<td>Time to 1st amb, days</td>
<td>16.6±7.9</td>
<td>13.1±11.9</td>
<td>-3.4 (-13.8-6.9)</td>
</tr>
<tr>
<td>Time to indep amb, days</td>
<td>39.0±18.7</td>
<td>27.0±22.5</td>
<td>-12.0 (-38.0-14.0)</td>
</tr>
<tr>
<td>Time from stand to indep amb, days</td>
<td>24.8±14.2</td>
<td>17.7±17.3</td>
<td>-7.2 (-28.2-13.9)</td>
</tr>
</tbody>
</table>

Abbreviations: amb, ambulation; a-PFIT-s, awakening Physical Function intensive care test score; indep amb, independent ambulation; mean diff, mean difference; MCID, minimally important clinical difference; SD, standard deviation; SOEOB, sitting on the edge of the bed; 95% CI, 95% confidence interval.

Footnote:
The p-value for statistical significance was calculated on matched pairs to determine the presence of statistical significance between groups. The data is on eight-matched pairs unless otherwise indicated.

Independent ambulation referred to patient being able to walk without needing hands on assistance from the therapist with/without a gait aid

1 Mean difference (95% CI) calculated on six matched pairs; with two pairs not included secondary to deceased prior to time-point of measurement.

** Mean difference > MCID of 1.5 points between control and intervention groups on awakening

*Significant result
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Parry, SM; Berney, S; Warrillow, S; El-Ansary, D; Bryant, AL; Hart, N; Puthucheary, Z; Koopman, R; Denehy, L

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