REVIEW

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Exercise rehabilitation following intensive care unit discharge for recovery from critical illness: executive summary of a Cochrane Collaboration systematic review

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Abstract

Skeletal muscle wasting and weakness are major complications of critical illness and underlie the profound physical and functional impairments experienced by survivors after discharge from the intensive care unit (ICU). Exercise-based rehabilitation has been shown to be beneficial when delivered during ICU admission. This review aimed to determine the effectiveness of exercise rehabilitation initiated after ICU discharge on primary outcomes of functional exercise capacity and health-related quality of life. We sought randomized controlled trials, quasi-randomized controlled trials, and controlled clinical trials comparing an exercise intervention commenced after ICU discharge vs. any other intervention or a control or 'usual care' programme in adult survivors of critical illness. Cochrane Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database, and Cumulative Index to Nursing and Allied Health Literature databases were searched up to February 2015. Dual, independent screening of results, data extraction, and quality appraisal were performed. We included six trials involving 483 patients. Overall quality of evidence for both outcomes was very low. All studies evaluated functional exercise capacity, with three reporting positive effects in favour of the intervention. Only two studies evaluated health-related quality of life and neither reported differences between intervention and control groups. Meta-analyses of data were precluded due to variation in study design, types of interventions, and selection and reporting of outcome measurements. We were unable to determine an overall effect on functional exercise capacity or health-related quality of life of interventions initiated after ICU discharge for survivors of critical illness. Findings from ongoing studies are awaited. Future studies need to address methodological aspects of study design and conduct to enhance rigour, quality, and synthesis.

Keywords Critical illness; Exercise rehabilitation; Exercise capacity; Health-related quality of life

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Introduction

Ever improving standards of care and improved patient selection for admission to the intensive care unit (ICU) are reducing rates of mortality amongst critically ill patients. However, as a consequence, the prevalence of impairment and disability among survivors has significantly increased. A substantial volume of longitudinal observational follow-up data has now characterized the profound impairments that survivors of critical illness experience for many years following ICU discharge across multiple domains including physical,[1–4] cognitive,[5–7] psychological,[8,9] and health-related quality of life.[10,11] In

addition, critical illness impacts on healthcare utilization and socioeconomic status[1,12,13] and can result in notable burden for family and caregivers.[14–16] Recently, an international multi-disciplinary stakeholder consensus assigned the term 'post-intensive care syndrome' to encompass the multi-faceted sequelae following critical illness.[17]

Intensive care unit-acquired weakness, stemming from the deleterious effects of peripheral skeletal muscle dysfunction secondary to critical illness, contributes to the persistent deficits observed in physical function. Significant muscle wasting has been observed to occur early, rapidly, and most severely in patients in multi-organ failure[18] and is one example of how peripheral skeletal muscle architecture can be affected.[19]

Rehabilitation is the cornerstone of management of post-critical illness morbidity,[20] and exercise-based interventions are advocated to target physical and functional disability. Ideally, rehabilitation should be delivered in a seamless pathway from ICU admission, transitioning to the ward, and following hospital discharge.[21] In the ICU, physical rehabilitation is typically characterized by early mobilization encompassing an increasingly functional hierarchy of activities ranging from bed-based exercises, sitting over the edge of the bed, standing, and ultimately walking. Adjunctive technologies including electrical muscle stimulation[22] and cycle ergometry[23] may also be employed. The safety and feasibility of early mobilization have been well documented,[24–28] and its efficacy has been examined in a number of systematic reviews demonstrating significant benefit in health-related quality of life, physical function, respiratory and peripheral skeletal muscle strength, length of ICU and hospital stay, and duration of mechanical ventilation.[29–32] However, the post-ICU discharge stages of recovery have been relatively under-examined, and given the residual impairments in physical function evident in ICU survivors, there is rationale for the ongoing delivery of exercise-based rehabilitation interventions.[30]

This paper provides an executive summary of a recent Cochrane Collaboration systematic review,[33] which synthesizes evidence for exercise-based rehabilitation initiated after ICU discharge. The aim was to determine the effectiveness of exercise-based rehabilitation, compared with usual care, on primary outcomes of functional exercise capacity and health-related quality of life in survivors of critical illness.

Methods

Eligibility criteria

Criteria for review entry were randomized controlled trials, quasi-randomized controlled trials, and controlled clinical trials that compared any exercise intervention initiated after ICU discharge vs. any other intervention or a control or 'usual care' programme in adult (≥18 years of age) survivors of critical illness who had been mechanically ventilated for 24 h or longer during an ICU admission.

Outcome measures

Primary outcomes were functional exercise capacity (with physical objective and/or subjective assessment) and health-related quality of life measured by reliable assessment scales. Secondary outcomes included rates of withdrawal, adherence and mortality, loss to follow-up, and adverse events.

Search strategy

Search strategies were based on a combination of controlled vocabulary and free-text terms related to the population and intervention. The following databases were searched from inception until 15 May 2014: Cochrane Central Register of Controlled Trials, Ovid SP Medical Literature Analysis and Retrieval System Online, Ovid SP Excerpta Medica Database, and the Cumulative Index to Nursing and Allied Health Literature. Searches were re-run in February 2015. Ongoing and studies pending classification were identified for inclusion in the update of the full review (scheduled 2017). We identified ongoing studies by using Clinical Trials (www.clinicaltrials.gov) and Current Controlled Trial (www.controlled-trials.com. isrctn/) registries and additionally searched the reference lists of included studies and the personal libraries of the review authors for additional potentially relevant studies. We contacted authors of studies where data were only available in abstract form to determine full publication status.

Data collection and analysis

The lead author (BC) initially screened results for de-duplication and removal of non-relevant subject material. Subsequently, two review authors (BC, and BO'N) independently screened firstly titles and abstracts, and then full-text versions of potentially relevant studies, and independently determined final eligibility by joint agreement by using a bespoke standardized form. Two review authors (LG and LS) independently extracted data pertaining to study design, participants, trial characteristics, intervention detail, and outcomes. Original authors were contacted for missing data. Two review authors (BB and LS) independently assessed risk of bias by using criteria outlined by the Cochrane Handbook for Systematic Reviews of Interventions.[34] Where a review author was the primary author of an included study (LS), data extraction and risk of bias were conducted by a different review author (BC).

Data management was performed by using RevMan, and the GRADE approach was used to assess the quality of the total body of evidence. Data were reported descriptively.

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Insufficient study numbers and heterogeneity across those included, precluded meta-analyses, subgroup and sensitivity analyses.

Results

We identified 4298 results of which 276 underwent title and abstract screening (*Figure* 1). Twenty two of these were reviewed in full-text format. Six studies were identified as eligible for inclusion in the qualitative synthesis, involving 483 participants.[35–40] Three studies were identified as ongoing[41–43] and a further three awaiting classification.[44–46]

Risk of bias was variable for all domains across all included trials (*Figure* 2). Risk of performance bias was high in all studies. For remaining domains, at least half of the studies demonstrated low risk of bias. One study was at high risk of selection bias, attrition bias, and other sources of bias. Risk of bias was unclear for the remaining studies across domains.

Exercise-based interventions in included studies were delivered on the ward in two studies: both on the ward and in

Figure 1 Flow diagram of study selection.

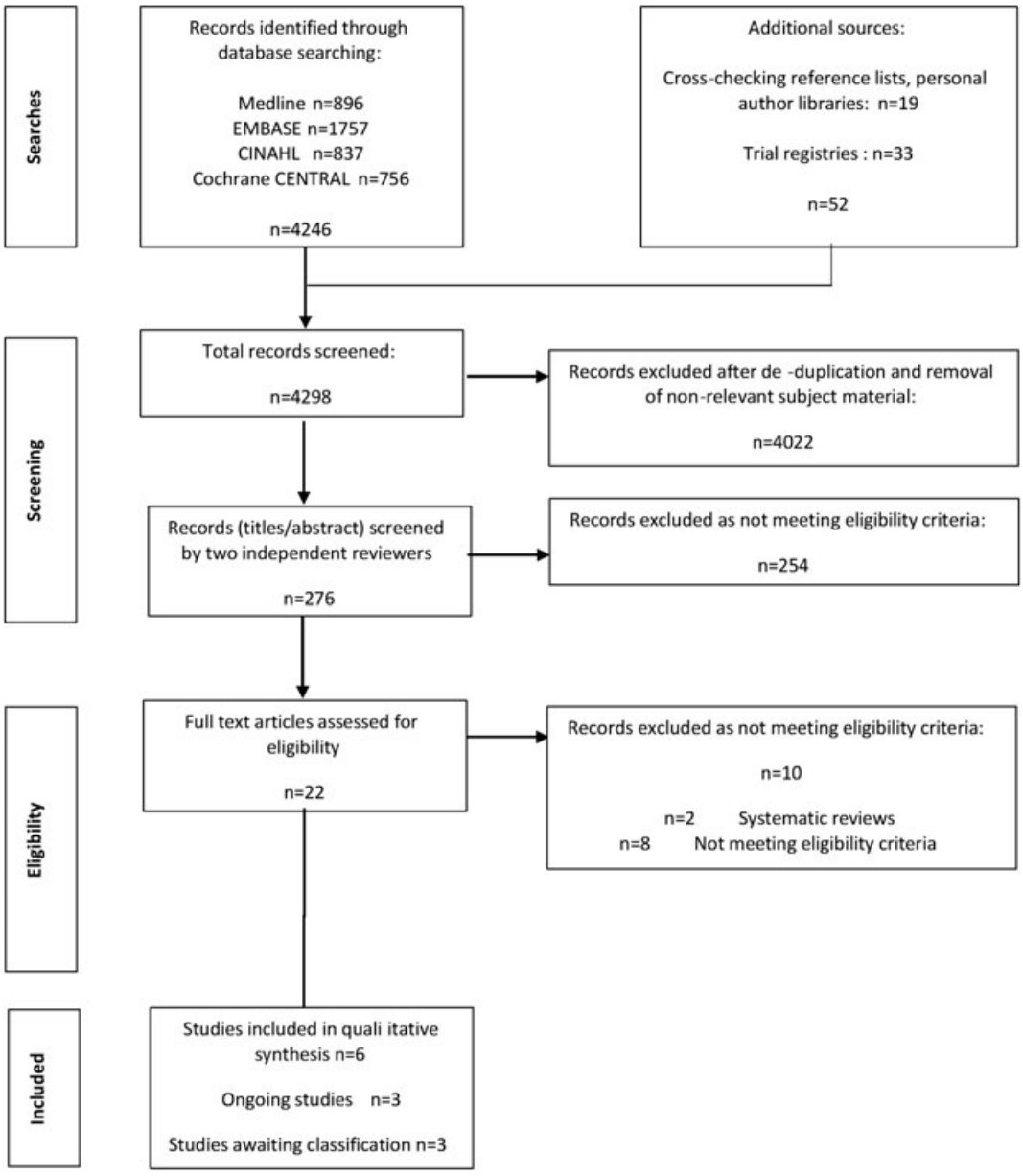

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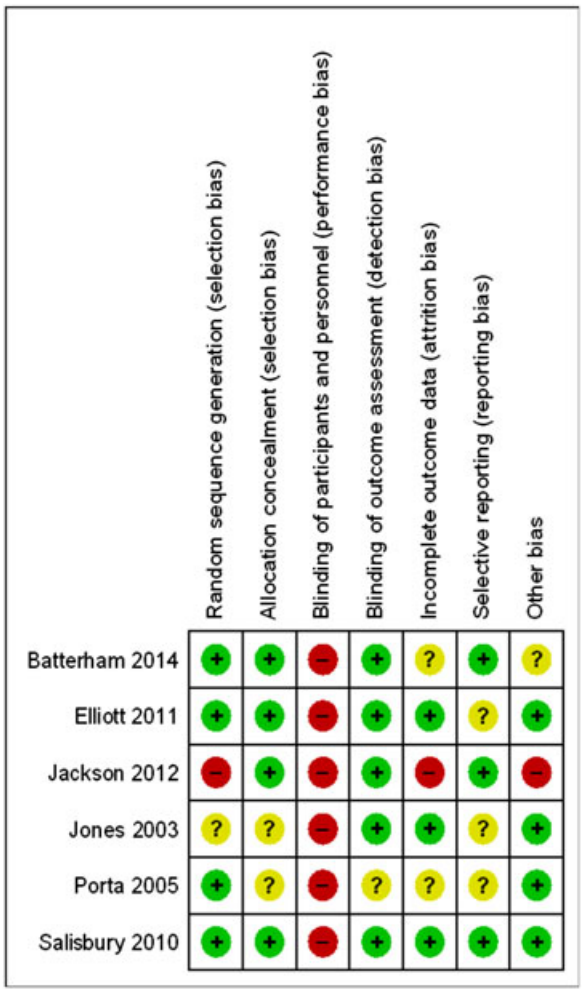
Figure 2 Cochrane Risk of Bias summary.



the community in one study and in the community in three studies, and were of variable duration. Control group participants in all included studies were documented as receiving standard practice care for post-critical illness management, albeit exact descriptions were limited (*Table* 1).

We were unable to undertake meta-analyses of data due to variability in study design, type and nature of interventions, outcome measures and associated metrics, and data reporting across included studies and therefore presented a narrative description of findings for individual studies for each outcome.

All six studies assessed functional exercise capacity. Overall quality of the evidence was very low. Individually, three studies reported positive results in favour of the intervention. Batterham *et al.*[35] found a small short-term benefit in anaerobic threshold [mean difference (MD) 1.8 mL O_2/kg/min, 95% confidence interval (CI) 0.4 to 3.2; *P* value = 0.02]. In a second study, both incremental (MD 4.7, 95% CI 1.69 to 7.75 W; *P* value = 0.003) and endurance (MD 4.12, 95% CI 0.68 to 7.56 min; *P* value = 0.021) exercise testing results were improved with intervention.[39] Finally, self-reported physical function increased significantly following use of a rehabilitation manual (*P* value = 0.006).[38] Remaining studies found no effect of the intervention.

Only two studies evaluated health-related quality of life, and neither study reported differences between intervention and control groups.[35,36]. Overall quality of the evidence was very low.

Four studies reported rates of withdrawal, which ranged from 0% to 26.5% in control groups and from 8.2% to 27.6% in intervention groups.[35–37,39] The quality of evidence for the effect of the intervention on withdrawal was low. Intervention adherence did not apply to control participants, and only one study made some reference to adherence rates in the intervention group,[35] and quality of evidence was very low. Quality of evidence for mortality was low, with mortality reported by all studies and ranging from 0% to 18.8%. Loss to follow-up, also reported in all studies and with low quality of evidence, ranged from 0% to 14% across all participants. Only one non-mortality adverse event was reported across all participants in all studies (a minor musculoskeletal injury), and the quality of the evidence was low.

Discussion

The aim of this Cochrane Review was to evaluate the effectiveness of exercise-based rehabilitation initiated after ICU discharge on functional exercise capacity and health-related quality of life in survivors of critical illness. We identified six completed and fully published trials for inclusion in the current review and six further pending trials that will be subsequently evaluated when the review is updated, indicating an expanding evidence base for this clinical field. Meta-analyses of findings were precluded due to quantity of data, and wide variability in characteristics of interventions and metrics of outcome measure selection and reporting, and hence, we were able to report a qualitative description of findings only. Consequently, we were unable to conclude the efficacy of post-ICU discharge exercise-based rehabilitation on our selected outcomes. Most included studies failed to show a significant difference between intervention and control groups. Where significant differences were evident, these were noted only in physiological outcomes following specific types of exercise training programmes, and which were non-generalizable. Methodological variation in intervention 'dose' and outcomes used for evaluating effectiveness was considered contributing factors to the non-significant differences seen between groups in the remaining studies.

The quality of the evidence was inconsistent. For most domains, low risk of bias ranged from 50% to 75%. All included

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Table 1 Summary of interventions evaluated in included studies

Study	Intervention characteristic			
	Delivery	Duration	Content	Follow-up
Batterham *et al*.[35]	Hospital-based, PT-supervised 2 × PT sessions/week 1 × unsupervised session/week	8 weeks	Cycle ergometry	Weeks 9 and 26
Elliott *et al.*[a36]	Home-based, self-delivered 3 × clinicians visits, 4 × TC	8 weeks	Endurance walk training; strength training	Weeks 8 and 26
Jackson *et al*.[37]	Home-based, 6 × clinician visits	12 weeks	Lower extremity functional exercise; endurance training	3 months
Jones *et al*.[38]	Home-based, self-delivered, 3 × TC/week	6 weeks	Rehabilitation manual and diary	Week 8 and 6 months
Porta *et al.* [39]	Hospital-based, clinician-supervised, 15 × daily 20 min sessions	Admission length of stay	Upper arm cycling	Discharge
Salisbury *et al.*[a40]	Hospital-based	Ward length of stay	Passive, active, and strengthening exercises, functional activities	3 months

[a]Detail provided of physical component only of rehabilitation package. Abbreviations: PT, physiotherapist; TC, telephone call.

studies demonstrated high risk of bias for blinding on participants and trial personnel, although it is acknowledged, such blinding in therapeutic rehabilitation trials can be pragmatically challenging. Notably, several studies reporting non-significant findings failed to meet intended sample size or were intended as pilot, feasibility studies to provide data to inform larger-scale trials; hence, these results could be attributable to type II error. Examination of screening and enrolment rates highlighted the challenges associated with recruitment into post-critical illness rehabilitation trials.

Conclusions

There was insufficient evidence to determine an overall effect on functional exercise capacity or health-related quality of life of an exercise-based intervention initiated after ICU discharge for survivors of critical illness. The degree of heterogeneity across included studies precluded a meta-analysis of data, and individual study findings were inconsistent with regards a beneficial effect on functional exercise capacity. No effect on health-related quality of life was reported. The methodological rigour of included studies was variable with risk of bias present in several domains. Results of ongoing studies, and those awaiting classification, will contribute to a further update of this Cochrane Collaboration systematic review. Future studies must address methodological aspects of identifying the target population, optimum dose of intervention, detailed characterization of usual care, and standardization of outcomes and reporting to enhance methodological rigour of investigations.

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Conflict of interest

B.C. is lead author of one study awaiting classification,[45] which may be included in a future update of the full review. L.S. is lead author of one included study.[40] L.S. did not extract data from this study nor check interpretation against the study report. L.S. is also a co-author of one study awaiting classification,[44] which may be included in a future update of this review. B.O'N. is lead author of one currently ongoing study,[43] which may be included in a future update of this review. L.G., A.D., M.P.W.G.: none known. N.H. is senior author for one study awaiting classification,[45] which may be included in a future update of this review. T.S.W. is senior author for one included study.[40] T.S.W. did not extract data from this study nor check interpretation against the study report. T.S.W. is also lead author for one study awaiting classification,[44] which may be included in a future update of this review. B.B. is co-author of a currently ongoing study,[43] which may be included in a future update of the full review.

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