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Improving rehabilitation after critical illness through outpatient physiotherapy classes and essential amino acid supplement: A randomized controlled trial☆,☆☆

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ABSTRACT

Purpose: Patients recovering from critical illness may be left with significant muscle mass loss. This study aimed to evaluate whether a 6-week program of enhanced physiotherapy and structured exercise (PEPSE) and an essential amino acid supplement drink (glutamine and essential amino acid mixture [GEAA]) improves physical and psychological recovery.

Materials and methods: Intensive care patients aged 45 years or older, with a combined intensive care unit stay/pre–intensive care unit stay of 5 days or more were recruited to a randomized controlled trial examining the effect of PEPSE and GEAA on recovery. The 2 factors were tested in a 2 × 2 factorial design: (1) GEAA drink twice daily for 3 months and (2) 6-week PEPSE in first 3 months. Primary efficacy outcome was an improvement in the 6-minute walking test at 3 months.

Results: A total of 93 patients were randomized to the study. Patients receiving the PEPSE and GEA had the biggest gains in distance walked in 6-minute walking test ($P < .0001$). There were also significant reductions in rates of anxiety in study groups control supplement/PEPSE ($P = .047$) and GEAA supplement/PEPSE ($P = .036$) and for GEAA supplement/PEPSE in depression ($P = .0009$).

Conclusion: Enhanced rehabilitation combined with GEAA supplement may enhance physical recovery and reduce anxiety and depression.

1. Introduction

During severe illness and immobility, skeletal muscle declines by 2% to 4% per day [1]. Muscle mass and function are also lost in a condition known as age-related sarcopenia. Individuals who are physically inactive can lose a significant amount of muscle mass after the age of 30 years; consequently, patients aged 45 years may already have lost almost 10% of their muscle mass before intensive care unit (ICU) admission, and those aged 60 years and over may be left with only 60% of the muscle of those younger than 30 years [2]. Rebuilding lost muscle requires the stimuli of exercise and nutrition [3]. Elderly individuals have a reduced sensitivity to the effect of amino acids on skeletal muscle protein synthesis [4], which is further compromised by immobility [5,6]. Their anabolic response to a protein-rich meal can be restored if a sufficient amount is given [7]; however, after illness, their intake may be poor. The stimulus of a meal to induce protein synthesis lasts 2 to 3 hours [8], so to increase the accretion of muscle per day, extra protein is given between meals. Essential amino acids (EAAs) are potent stimuli for muscle rebuilding [9], do not impair subsequent meal intake, and prevent loss of muscle in elderly glucose-intolerant patients [10]. Elderly subjects older than 65 years with reduced physical activity given 12-g EAA 3 times a day for 3 months increased their physical capacity and the 6-minute walk test distance (6MWT) [11]. In elderly subjects with reduced muscle mass, a supplement of 8-g EAA over 60 weeks improved their lean body mass and insulin sensitivity [12]. Another amino acid glutamine is considered conditionally essential in critically ill patients [13,14], and its replacement improves survival [15]. In the most severely ill, the supply may become limiting late in the illness [16]. Glutamine also improves insulin sensitivity acutely [17], and in healthy adults, it improves insulin action postmeal [18]. Immobility reduces the stimulatory benefit of EAA [19], so it is logical to combine it with a physical rehabilitation program.

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A follow-up study of adult respiratory distress syndrome patients showed that muscle weakness is a major determinant of outcome with a time scale of recovery measured in months and years [20]. Rehabilitation also needs management of any psychological problems [21,22]. Previous research using a 6-week rehabilitation program of advice and exercises, the ICU Recovery Manual, showed an improvement in physical functioning after critical illness [23]. In our pilot study, 38 ICU survivors underwent physiotherapy-led outpatient rehabilitation program, involving 2 hours of supervised exercise and education sessions each week and 2 unsupervised exercise sessions each week for 6 weeks. Both exercise capacity and anxiety and depression scores were improved [24].

The study hypothesis is that a supplementary glutamine and EAA mixture (GEAA) taken between meals combined with early physiotherapy and program of enhanced physiotherapy and structured exercise (PEPSE) will enhance physical recovery post-ICU. The study examined the effect of the GEAA supplement and PEPSE on the physical recovery in ICU patients 45 years or older.

2. Materials and methods

2.1. Protocol

The study was conducted in 2 hospitals in the UK: Whiston Hospital and Manchester Royal Infirmary. A third hospital, Milton Keynes, was added to the study to increase recruitment but did not recruit any patients. Ethical approval was obtained from the Wales 5 ethics committees for all centers, and the research was carried out in compliance the 1964 Declaration of Helsinki, its later amendments, and the need for informed consent.

The inclusion criteria were that patients should be aged 45 years or older, had a combined ICU and pre-ICU stay of 5 days or more, and able to undertake the physiotherapy program. Patients were excluded if they were (*a*) younger than 45 years; (*b*) had a combined ICU and pre-ICU stay of less than 5 days; (*c*) unable to undertake physiotherapy (assessed by an experienced physiotherapist); (*d*) unable to take the nutritional supplement drink; (*e*) too confused to give informed consent (including traumatic brain injury); (*f*) discharged for palliative care; (*g*) had malignant disease if not surgically removed and not discharged for palliative care or chemotherapy, growth stimulation of the amino acid mixture is not tissue specific and its effect on an untreated or nonoperative tumor cannot be predicted; or (*h*) had persistent nonrecovering severe liver failure or renal failure (requiring regular dialysis).

The power was calculated for each factor based on available data for the 6MWT. For PEPSE, data from observational studies and pilot work were used to make estimates. Six-minute walking test data from Herridge et al [23] showed that adult respiratory distress syndrome patients at 3 months post-ICU could manage 281 m and by 12 months 422 m (interquartile range, 277-510 m) (66% of predicted norm), a difference of 141 m without any rehabilitation. Earlier rehabilitation work [11] showed a physical improvement with a 6-week self-help package at 6-month follow-up of approximately 15% in functional score using the physical function scores of the Short Form 36 (SF-36). The PEPSE pilot showed more than a 50% improvement from 279 m (SD, 107 m) to 424 m (SD, 110 m) by 3 months, a difference of 145 m with an SD of 110 m [24].

Herridge et al [23] showed a change of 141 m without rehabilitation over 9 months. If we assume that 50% of this recovery occurs in the first 3 months without any support and that the self-help package adds a further 10% in the first 3 months, it is estimated that the control group will improve by 60% (84 m) of 141 m over the 3-month study period. The difference between the control and treatment groups will be 58 m (40% of 145 m), and this gives a sample size for each group of 35 subjects. The nutrition effect [14] in which elderly subjects with reduced physical activity had an EAA supplement over 3 months showed increases in 6MWT to 269 m (SD, 35) vs 212 m (SD, 40) in control group. This gives a sample size of 10 subjects, but because this was not in the same group of patients and is smaller than that for physical exercise, it is discounted. To allow for loss in each group, we required 45 subjects giving a total recruitment target of 180 patients into the 2 × 2 study (Power 0.8, $\alpha = .05$).

3. Treatment conditions

This is a 2 × 2 factorial design randomized controlled study, with the nutrient double blind and the physiotherapy single blind to assessment (see Fig. 1).

3.1. Study start

Patients were screened for recruitment once discharged from level 3 (ICU) to level 2 (high-dependency care). Those meeting the inclusion criteria were consented and had baseline assessments of prior physical and mental status and randomized to 1 of 4 study arms (see Fig. 1), having achieved the minimum level of physical capability (level 2, sit on edge of bed). The nutrition supplement or control was commenced immediately, and all received the ICU Recovery Manual [11].

4. Primary study end point

The patients were assessed at the start of the study and at 3 months of follow-up using 6MWT [25], which is a widely used and validated assessment of exercise capacity and conducted using standard American Thoracic Society guidelines [25].

When subjects reached the minimum physical level to start active rehabilitation level 6 (able to cover 30 m walking) (see flow chart Fig. 1), they commenced either the PEPSE with the self-directed exercises in the ICU Recovery Manual or the self-directed exercises alone (control).

4.1. Nutritional intervention GEAA

The nonmedicinal food supplement was double blind using identical powder mixtures in sachets formulated and supplied for this study by the nutrition company, Fresenius Kabi Deutschland GmbH. The GEAA is based upon commercial nutritional whey protein sources and was formulated for oral use, each drink (dose) containing 10.32-g EAA, 12.3-g conditionally EAAs (includes 10-g glutamine) and 4.4-g non-EAAs. The ratio of leucine to other amino acids was 0.15:1. Patients were instructed to mix each sachet with 200 mL of water, and they consumed either flavored GEAA or a similar tasting control low-calorie drink within 1 hour of physical activity. Instructed to be taken as a supplement twice daily, it gave a daily supplement of 20-g EAA and 20-g glutamine for 3 months additional to their diet.

4.2. Physiotherapy intervention PEPSE

All patients received early active physical therapy and mobilization throughout their hospital stay. The control group used the 6-week ICU Recovery Manual, which is a patient-controlled self-help rehabilitation program. This incorporates an educational self-help program to address psychological issues and a self-guided exercise program. The PEPSE comprised a 6-week program of supervised physiotherapy sessions, in addition to the self-help program, which started when the patients are physically able. Within the hospital, this was delivered 3 times weekly and then continued on a weekly basis in the form of a structured rehabilitation class after hospital discharge. Program of enhanced physiotherapy and structured exercise supervised sessions were run by senior critical care physiotherapists in a gymnasium. Initial assessment included a full review of subjects' cardiorespiratory and musculoskeletal systems to ensure patient safety.

An interval approach to training was used, and each exercise session consisted of a circuit of 10 stations, with participants

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