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Effect of intermittent or continuous feed on muscle wasting in critical illness: A phase II clinical trial

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SUMMARY CONFLICT OF INTEREST STATEMENTS:

DEB has received speaker fees, conference attendance support or advisory board fees from Nutricia, Baxter, BBraun, Nestle Nutrition, Fresenius Kabi, Abbott Nutrition, Cardinal Health and Avanos. ZP has received honoraria for consultancy from GlaxoSmithKline, Lyric Pharmaceuticals, Faraday Pharmaceuticals and Fresenius-Kabi and speaker fees from Orion and Nestle. HM holds patents relating to intravenous hydration and to regulation of metabolic efficiency using renin-angiotensin system antagonists and consults for Google Health. MW has accepted accommodation and attendance at educational meeting organised by Orion. Other authors have no conflicts of interest to declare.

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body Mass Index; CF: Continuous feeding; IF: intermittent feeding; ICU: Intensive Care Unit; ICC: Intraclass Correlation Coefficient; RF_{CSA}: Rectus Femoris cross-sectional area; SOFA: Sequential organ failure assessment.

Abstract

Background: Acute skeletal muscle wasting in critical illness is associated with excess morbidity and mortality. Continuous feeding may suppress muscle protein synthesis as a result of the muscle-full effect, unlike intermittent feeding which may ameliorate it.

Research Question: Does intermittent enteral feed decrease muscle wasting compared with continuous feed in critically ill patients?

Study Design and Methods: In a Phase II interventional single-blinded randomized controlled trial, 121 mechanically-ventilated adult patients with multi-organ failure were recruited following prospective informed consultee assent. They were randomized to the intervention group (intermittent enteral feeding from six four-hourly feeds per 24 hours, n=62) or control group (standard continuous enteral feeding, n=59). The primary outcome was ten-day loss of rectus femoris muscle cross-sectional area determined by ultrasound. Secondary outcomes included nutritional target achievements, plasma amino acid concentrations, glycaemic control and physical function milestones.

Results: Muscle loss was similar between arms (-1.1% (95%CI -6.1, -4.0); p=0.676). More intermittently fed patients received 80% or more of target protein (OR 1.52 (1.16-1.99); p<0.001) and energy (OR 1.59 (1.21-2.08); p=0.001). Plasma branched-chain amino acid concentrations before and after feeds were similar between arms on trial day 1 (71 μM (44-98); p=0.547) and trial day 10 (239 μM (33-444); p=0.178). During the 10-day intervention period the coefficient of variation for glucose concentrations was higher with intermittent feed (17.84 (18.6-20.4) versus continuous feed (12.98 (14.0-15.7); p<0.001). However, days with reported

hypoglycaemia and insulin usage were similar in both groups. Safety profiles, gastric intolerance, physical function milestones and discharge destinations did not differ between groups.

Interpretation: Intermittent feeding in early critical illness is not shown to preserve muscle mass in this trial despite resulting in a greater achievement of nutritional targets than continuous feeding. However, it is feasible and safe.

Clinical Trial Registry: www.ClinicalTrials.gov: NCT02358512

Introduction

Acute skeletal muscle wasting occurs rapidly in critical illness, and contributes to increases in length of stay, mortality and functional disability[1-4]. This in turn has significant detrimental impacts on patients, carers, and health service utilisation post-discharge. This disability has proven resistant to exercise rehabilitation[5-8] or goal-directed nutrition[9] interventions, highlighting the need for primary prevention.

Decreased muscle protein synthesis is a major pathophysiological component of muscle wasting [1,10], and continuous feeding (CF) may contribute to this. Continuous provision (and continuously raised concentrations) of amino acids suppresses myofibrillar protein synthesis (the muscle-full effect[11]), demonstrated in both enteral[12] and parenteral amino acid delivery[13].

Conversely, peaks in amino acid concentration (leucine in particular[14]) promote anabolism[15], and intermittent feeding of critically ill patients might therefore be advantageous.

Intermittent feeding (IF) increases splanchnic blood flow and results in pulsatile changes in ghrelin, insulin and peptide YY concentrations[16], which may increase amino acids availability, further stimulating muscle protein synthesis.

For these reasons, studying the benefits of IF in the critically ill has been strongly advocated[17] as this may offer a more efficacious form of acute nutrition support [18] and decrease the development of disability[19].

We hypothesized that IF would abolish the muscle-full effect, and therefore ameliorate acute skeletal muscle wasting. This in turn may influence length of Intensive Care Unit (ICU)/hospital stays, time on mechanical ventilation, Health-related Quality of Life scores, functional ability and gut-to-plasma amino acids

transfer. The study was performed specifically in patients at risk of persistent critical illness, as these patients suffer from significant muscle wasting[1], are at greatest risk of subsequent functional disability and less likely to return home[20,21].

Methods

This was a multicentre, single-blinded randomized controlled Phase II trial conducted in eight mixed United Kingdom ICUs, with an allocation ratio of 1:1. Basic characteristics of the ICUs are shown in e-Table 1.

Participants

Participants qualified for enrolment up to 24 hours after ICU admission.

Inclusion Criteria: Adult (>18 years), expected to be intubated and ventilated for ≥48 hours; requiring enteral nutrition via nasogastric tube; multi-organ failure (Sequential Organ Failure Assessment (SOFA) score[22] >2 in ≥2 domains at admission); likely ICU stay ≥7 days and likely survival ≥10 days (assessed as previously by senior ICU clinicians[1]).

Exclusion criteria: Pre-Randomization enteral feeding on the ward or >12 hours on ICU; unlikely to meet nutritional requirements by 72 hours using a standard feeding schedule (based on predicted clinical trajectory); need for sole/supplemental parenteral nutrition or post-pyloric feeding on ICU admission. The full list of exclusions is available in the Supplementary Material.

Prospective informed assent was obtained in writing from a nominated personal consultee or professional consultee. Retrospective participant consent was obtained on return of participant's mental capacity. Permission to use participants' data if

capacity did not return or they did not survive was included in the assent process.

The study received ethics committee approval (National Research Ethics Service Committee London – Queens Square; REC reference 14/LO/1792; IRAS project ID 160281) and was publicly registered prior to the first patient being randomized (ClinicalTrials.gov, NCT02358512). We used the CONSORT (Consolidated Standards of Reporting Trials) statement when reporting this trial[23].

Feeding regimens

Enteral feeding was allowed for up to 6 hours pre-randomization. The same IF regimen (intervention) was used at every site, consisting of six four-hourly feeds during 24 hours[24], administered via nasogastric tube using a syringe over 3-5 minutes. Depending on each Trust's Approved Supplier, either Ensure Compact (energy content: 2.4kCals/ml; protein content: 0.104g/ml; Abbott Nutrition, Chicago, Illinois, US) or Fortisip Compact Protein (energy content: 2.4kCals/ml; protein content: 0.144g/ml; Nutricia, Hoofddorp, The Netherlands) were used, with a range of starter bolus sizes of 60-80mls according to the participants' initial individual nutritional targets. The CF regimen (control) consisted of the total volume of feed administered over 24 hours, as per local feeding protocols.

The specific feed used for each patient in either arm of the trial was prescribed by each ICU's dietitian at a dose which was calculated to meet that patient's nutritional needs. Further details of the feeding protocols are described in the Supplemental Material and e-Figures 1 and 2.

Nutrition targets were individualized by each unit's dietitian within 72 hours of randomization. The Modified Penn State equation or a weight-based equation (e.g.

25 kcal/kg) was used to estimate energy targets. Protein targets were individualized with a minimum of 1.2 g/kg being used (actual body weight if BMI <30 and ideal body weight if BMI > 30). After the intervention period, participants reverted to continuous feeding if enteral feed was required. Deviations from prescribed nutritional delivery (and their rationale) were recorded. The adequate nutritional threshold was set at >80% of prescribed targets[25]. Analysis was further performed on those achieving >60%, in keeping with international practice[26].

Endpoints

The primary endpoint was change in Rectus Femoris cross-sectional area (RF_{CSA}) at trial day 10[1]. This method is fully validated for use in the critically ill [1], and was chosen as an outcome given the difficulties with volitional measures of physical function in acute critical illness[27]. Using B-mode ultrasound [1], RF_{CSA} was measured on trial days 1, 7 and 10 following randomization and at ICU and hospital discharge. Members of the research team were trained to perform RF_{CSA} measurements, and scan quality at each site was deemed adequate with an Intraclass Correlation Coefficient (ICC)>0.9. Full details are provided in the Supplemental Material.

Secondary endpoints and their method of assessment are listed in Table 1. Blood samples were taken on trial days 1, 7 and 10. Plasma concentrations of 21 amino acids (including branched chain and non-branched chain) were determined immediately before and 30 minutes after intermittent feeds at 9:00 and 13:00 in the intervention arm and at equivalent timepoints in the control arm. Plasma concentrations of Citrulline (a marker of gut integrity[28]) were additionally measured.

Measures of adverse safety impacts included proven or suspected aspiration, increased daily rates of vomiting or diarrhoea (Bristol Stool Score ≥5[29]), gastric residual volume (GRV)≥300ml, or impaired glycaemic control from four-hourly glucose measurements. Normoglycaemia was defined as a blood glucose concentration of (4-10mmol/l) and thus concentrations of ≥10.1 or ≤3.9mmol/l as hyperglycaemia or hypoglycaemia respectively. Daily variation in blood glucose concentration was assessed by the Coefficient of Variation (mean/standard deviation)[30].

Sample size

Patients with multi-organ failure suffer a 21.5% (SD 10.6) reduction of RF_{CSA} in 10 days [1]. A sample of 26 per group would give 90% power to detect a 10% difference between groups, at the 1% significance level. We performed a stratified analysis to allow for the different response of patients with pre-existing chronic disease (defined as a stable chronic health condition requiring primary or secondary care follow-up) [31,32], estimating the proportion of chronic disease:non-chronic disease participants in the study cohort to be 2:1. A sample size of 29 per group would detect a large interaction effect (f=0.4) for a factor with a 2:1 ratio of subgroups with 80% power at the 5% level [33]. Identifying those patients at risk of persistent critical illness is challenging, and a high drop-out rate was expected from both early death and early recovery. We aimed to recruit at least 116 patients to allow for a dropout rate and protocol violations (common in many critical care trials) of up to 50%, with increased recruitment allowed to ensure equal numbers per arm.

Randomization and blinding

Randomization was stratified for recruitment site (1:1 basis), and for the presence of chronic disease and occurred once assent was obtained. Treatment group allocation

used an independent remote electronic web-based random allocation service to generate an unpredictable allocation outcome, and to conceal that outcome from research staff until assignment occurred. ZP (who assessed all ultrasound scans for the primary outcome) and the data analysts were masked to allocation until data analysis was complete (see Supplemental Material).

Statistical analyses

The statistical plan was designed by a statistician (JAC), and approved *a priori* as part of the process of obtaining ethical approval. Further details are available in Supplemental Material.

Both Intention-to-Treat and Per Protocol (those that spent 10 days in ICU and had their muscle mass measured) cohorts were analysed. We compared results between groups using analysis of variance (ANOVA) with subgroup analysis by presence of chronic disease states. An adjustment for a small number of pre-specified prognostic covariates (admission bicarbonate and ratios of PaO_2/FiO_2 [1]) was made using analysis of covariance (ANCOVA).

A change in RF_{CSA} of -21.5% (as per power calculation) was assigned to those patients who were lost to follow up or had their intervention discontinued[9] in the Intention-to-Treat analysis. Sensitivity analyses were performed with i) score assignment of -0% at 10 days, ii) multiple imputation and iii) the per-protocol subgroup.

All data were assessed for normality using D'Agostino and Pearson omnibus normality tests. Data were then analysed using Student's t-test, Pearson's coefficient, Mann-Whitney U test and Wilcoxon's signed Rank Tests as appropriate.

Area under the curve was used as a measure of amino acid concentration[34]. Glucose variability was described using the coefficient of variation[30]. Differences in nutritional delivery were assessed using Fisher's exact test. Fragility indices, describing the robustness or its lack ('fragility') of a clinical trial's results, were calculated. These indicate how many additional patients would be required in order for statistically significant results from a trial to be rendered non-significant [35]. Two-tailed t-tests were used, and statistical significance was indicated by $p \leq 0.05$.

Results

Between 9th February 2015 and 12th September 2017, 3487 patients were screened, of whom 2926 were ineligible. Of these, 998 patients (29.7%) were not expected to be intubated for 24 hours or more, 305 (9.1%) had single organ failure (SOFA score <2 in two or more domains), and 307 (9.1%) were not expected to survive for 10 days. Of the 561 patients meeting inclusion criteria, 127 patients were randomized; 394 patients were unable to be recruited due to shortage of research staff, primarily outside the weekday recruitment period. Five were withdrawn prior to feed commencing and 1 randomized in error, leaving 121 randomized: 62 in the intervention and 59 in the control group. Ethical approval was given to increase recruitment so that randomization could continue until the minimum number per arm (determined *a priori*) was met (see Supplemental Material).

A total of 63 patients completed the 10-day trial period (Figure 1); reasons for premature withdrawal are shown in e-Table 3. Participants' demographics were not different between trial arms (Table 2).

Change in muscle mass

No difference in loss of RF_{CSA} was seen between intermittent and continuous arms at 10 days (-1.1% (95%CI -6.1, -4.0); p=0.676, Figure 2 and e-Figure 3). This lack of difference between groups persisted following adjustment for age, PaO_2/FiO_2 ratio, bicarbonate and chronic disease at trial day 10 (-1.8% (95%CI -6.3, 2.7); p=0.429). Chronic disease states were not associated with any difference in muscle wasting (effect size: -3.2 (95%CI -12.6, 5.5); p=0.505) (e-Tables 6 and 7). These results did not differ with any of the three sensitivity analyses (e-Table 8).

Nutritional Delivery

Data were available for 441 days of enteral feeding received by participants in the IF arm and 413 days received by those in the CF arm. Patients received a similar number of days of nasogastric feeding in both arms (4 days (range 0-10) versus 4 days (range 0-10); p=0.576), (not necessarily contiguous) due to a variety of clinical and logistical reasons for disruption of nutritional delivery (see e-Table 9). The IF regimen resulted in greater nutritional delivery for both protein (80.3% (95%CI 77.3-83.4) versus 69.9% (95%CI 66.6-73.1); p<0.001) and energy (82.4% (95%CI 79.2-85.6) versus 72.5% (95%CI 69.3-75.7); p<0.001) relative to nutritional targets. More patients met the 80% protein threshold with IF (57.0% versus 46.5%; OR1.52 (95%CI 1.16-1.99; p<0.001; fragility index=15) and the 60% threshold (78.6% versus 65.9%; OR 1.89 (95%CI 1.4-2.6); p<0.001; fragility index=28). Energy thresholds were similarly affected at 80% (63.0% versus 51.6%; OR 1.59 (95%CI 1.21-2.08); p=0.001; fragility index=19) and 60% (80.5% versus 69.0%; OR 1.83 (95%CI 1.34-3.50); p<0.001; fragility index=24) thresholds (Figure 3A and B, e-Table 9). Between-group differences were similar or greater in the Per Protocol analysis (e-Tables 11 and 12).

No difference was seen in days of adequate nutrition prescribed and delivered between arms (n=111; 86.6% versus 85.4%; p=0.681). Feeding interruptions and/or missed feeds occurred 157 times in the IF arm and 156 times in the CF arm. IF was less disrupted by airway management (12 (7.6%) versus 27 (17.3%); p=0.017), or intolerance secondary to vomiting (5 (3.2%) versus 16 (10.3%); p=0.019) or diarrhoea (0 (0.0%) versus 4 (2.6%); p=0.050). IF was more likely to be disrupted for abdominal distension (5 (3.2%) versus 0 (0.0%); p=0.021) and was more likely to have feed prescription or delivery errors (14 (8.9%) versus 2 (1.3%); p=0.001) (e-Table 9).

Plasma amino acid concentrations

Amino acid profiling was performed for 329 time-points. Change in plasma concentrations of branched-chain amino acids before and after feeds did not differ between arms on trial days 1 (71 μM (95%CI 44-98); p=0.547), 7 (90 μM (95%CI 57-122); p=0.587) or 10 (239 μM (95%CI 33-444); p=0.178; e-Figure 4). Neither did non-branched chain amino acids or citrulline concentrations differ at any time-point (p>0.05 in both cases, e-Figure 5).

Plasma concentrations of leucine (the major stimulant of muscle protein synthesis) over time exhibited a sinusoid waveform in the IF arm (Figure 4ABC) sufficient to stimulate protein synthesis [14].

Safety

The coefficient of variation for plasma glucose concentrations was higher in the intermittent than in the control arm (17.84 (95%CI 18.6-20.37) versus 12.98 (95%CI 14.0-15.7); p<0.001, Figure 4D). There was no difference in the number of days in which hypoglycaemic (≤3.9mmol/l) episodes occurred (0.0% (95%CI 0.0%-0.0%)

versus (0.0% (95%CI 0.0%-0.0%); p=1.00) between groups. More days with a reported hyperglycaemic (≥10.1mmol/l) episode were seen with IF compared with CF (50.0% (95%CI 33.3-72.7) versus 33.3% (95%CI 18.2-50.0); p<0.001). Differences in the total number of episodes of hyperglycaemia (280 versus 192 in IF versus CF groups, respectively) appear to have been driven by a few individuals (Figure 4E). While cumulative insulin use was no different between groups 0.0iu (range 0-1582iu) versus 0.0iu (range 0-1403); p=0.697), IF patients received less exogenous insulin on trial days 8-10 than CF patients (Figure 4F).

There were no differences between IF and CF arms in trial days with diarrhoea (35.9% (95%CI 27.95-43.9%) versus 28.1% (95%CI 20.9%-35.3%); p=0.198), vomiting (0.8% (95%CI 0.2%-1.8%) versus 3.7% (95%CI 0.8%-6.6%); p=0.104) or use of prokinetics (13.8% (95%CI 6.3%-21.3%) versus 20.8% (95%CI 13.0%-28.7%); p=0.115). There was no difference in trial days with reported GRVs >300ml (16.1% (95%CI 10.0%-22.2%) versus 21.3 (95%CI 14.6%-28.0%); p=0.230). Seven Adverse Events (e-Tables 13 and 14) were reported in the intermittent arm and 3 in the continuous. Two from the former group (erratic glucose levels in patients with diabetes mellitus) were considered probably or possibly as secondary to the intervention.

One patient was transferred from the intermittent to the continuous arms with no clear reason following consultant physician review. Three were transferred from the continuous arm to either parenteral nutrition or nasojejunal feed for GRVs>300ml (e-Table 3).

Physical function milestones and Health-Related Quality of Life

Of the 87 patients who survived to ICU discharge, 39 (44.8%) had a first sit-to-stand time recorded and 38 (43.7%) had a first transfer from bed-to-chair time recorded. There was no difference in sit-to-stand (1 day (95%CI -4 to +6) versus 2 days (95%CI -5 to +1); p=0.324) or first transfer (2 days (95%CI -4 to +3) versus 1 day (95%CI -5 to +2); p=0.868) before ICU discharge between arms. Data for 6-minute walking distance, Short Physical Performance Battery and Health-Related Quality of Life (pre- and post-ICU) were collected in only 11 (9.1%) participants for each of the first two outcomes, and 56 (46.3%) and 3 (2.5%) of participants for the last two outcomes, due to an unexpected lack of staff resources; these data were not included in the analysis. Primary care cost data proved not feasible to collect due to research staff shortage and are not reported.

Discharge destination

No difference was seen in rates of discharge to home as opposed to rehabilitation or nursing facilities between arms (24 (39.3%) versus 32 (54.2%) respectively, p=0.123). Further data are available in the Supplemental Material.

Discussion and Interpretation

We performed a multicentre, assessor-blinded randomized trial comparing an intermittent with continuous enteral feeding in critically ill with multi-organ failure and at risk of prolonged intensive care stay. IF increased nutritional target achievement, was safe, tolerated and feasible but did not result in amelioration of acute skeletal muscle wasting. As a likely consequence, no differences were seen in either physical function milestones or in discharge destination between groups. Plasma concentration of amino acids and markers of intestinal function and absorption did

not differ between groups, although the IF regimen resulted in peak leucine concentrations sufficient to stimulate protein synthesis, unlike CF [14,36].

These data demonstrate that IF over the first 10 days of ICU admission, as a sole intervention in critically ill patients with multi-organ failure, does not prevent muscle wasting or improve time to achieving physical function milestones. This is in keeping with new data suggesting that success of any intervention might be dependent upon the contemporaneous suppression of intramuscular inflammation[37,38] and addressing bioenergetic failure[37], both of which hinder muscle anabolism.

Better nutritional delivery from IF has been hypothesized[39], and observed in small studies[40]. These data demonstrate in >800 feeding days of critically ill patients, that IF allows nutritional targets to be met more effectively. The fragility index was higher than those reported for other critical care trials[35,41], allowing confidence in these data.

In keeping with previous studies[42,43], the IF regimen was feasible and safe. Whilst no disparities in hypoglycaemia incidence were seen, the increased variability of blood glucose levels with IF may require more bespoke insulin protocols for those patients with greater insulin resistance. The corollary of this is that a decrease in insulin use on trial days 8-10 with IF was observed, likely reflecting the increase in insulin resistance associated with continuous amino acid availability[44].

Our study has several strengths including that of the randomized multi-centre design and blinding of primary outcome by separating data acquisition (at site) from data analysis (blinded, centrally performed). Standardised teaching of RF_{CSA} data collection and independent assessment of data quality allows us to be confident in the results of our trial. We further adjusted for known risk factors of muscle wasting

(age, PaO_2/FiO_2 ratio, bicarbonate and chronic disease), increasing the validity and generalisability of our data.

We studied those at risk of a prolonged intensive care stay[45], who face a greater risk of death, prolonged hospital stay, and disproportionate use of health resources compared to patients without persistent critical illness[21]. Studying this population allowed more effective intervention delivery in those patients in whom the primary outcome was measured. Despite this being a particularly challenging group to study, a per-protocol analysis was achieved in 50% of patients randomized over 8 sites, a similar proportion to another recent nutritional interventional trial[9] and sufficient for our *a priori* power calculation.

The presence of a chronic disease can affect response to interventions[31] and can alter metabolism differentially[37]. No interaction was seen between the presence of a chronic disease and intervention response. The role of chronic disease status and response to nutritional interventions remains unclear.

Data are conflicting as regards to protein adequacy affecting muscle mass and physical function positively[46] or negatively[1,47,48] Similarly differential energy intake has yet to be proven to affect muscle mass or physical function[49]. Hence it remains unclear as to whether the difference in nutritional delivery would affect the primary outcome. Nutritional delivery was not an *a priori* factor for adjustment, for the reasons detailed above, unlike those chosen that have supportive data[1].

Our study does have several limitations. For logistic reasons, we could not blind staff at local sites to the allocated nutritional protocol, but this would not result in systematic bias. However, the single central scan assessor was blinded to treatment allocation. Each site used their local CF protocol as per Trusts' nutritional guidelines,

although protocols are highly comparable and a level of careful pragmatism was accepted, to allow generalisability. The weakness of predictive equations for deriving energy expenditure has been recognised recently[50], and indirect calorimetry will be considered in future studies as available and appropriate. Recording of physical function and health-related quality of life data was inconsistent. The use of functional outcomes in nutritional research remains novel[51], and the process of data collection will inform future trials. Funding was not available for recruitment and nutritional assessment over weekends. While the emergency admission case-mix in the UK does not differ between weekdays and weekends[52], future pragmatic trials might seek to make daily recruitment possible.

Finally, while we studied a mix of different disease states, current evidence suggests muscle wasting is determined by severity of organ failure, not admission diagnosis, with similar rates seen in unselected populations[1,53], and in selected populations such as trauma[54], ECMO support[55] or tetanus[56]. The patients we chose to study (likely to have a length of stay >10 days) constitute only approximately 16% of the critically ill population[21]: It is possible that such a group have the greatest resistance to any mitigating intervention. The temporal relationship of interventions with muscle mass preservation remains relatively unknown in the critically ill patient[57]. Further, longer periods of nutritional interventions are likely needed for differences in muscle mass to become apparent.

In future trials IF may still have a role as a co-intervention with others intended to increase muscle protein synthesis (such as metabolic modulators or anti-inflammatory interventions), as the observed branched-chain amino acid concentration peaks are sufficient to stimulate protein homeostasis in healthy individuals[14]. Specifically, IF may lower the amount of resistance exercise necessary

to induce an anabolic effect, and therefore combined interventions might be studied[58,59]. IF may also help establish a normal circadian rhythm for these patients, and may be included in trials of interventions intended to have this effect[60].

Secondly, a role for IF in the optimisation of nutritional delivery needs to be explored, as this may be a pragmatic, inexpensive, safe and easily implemented method of ensuring patients receive the nutrition they require.

To conclude, in this trial intermittent enteral feeding in early critical illness does not preserve muscle mass as a sole intervention. However, it is feasible and safe, and results in a greater achievement of nutritional targets than a continuous feeding regimen.

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HEM has a patent 'The use of inhibitors of the renin-angiotensin system' which relates in part to the prevention of muscle wasting, issued.

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Tables

Secondary Endpoint	Method of Assessment	Personnel
Change in muscle mass between trial day 7 and trial day 1	Ultrasound-derived Rectus Femoris cross-sectional area	Investigator
Length of ICU stay	Electronic/paper clinical records	Investigator
Length of hospital stay	Electronic/paper clinical records	Investigator
Days of mechanical ventilation	Electronic/paper clinical records	Investigator
Amino acid concentrations (including citrulline)	Biochemical analysis plasma samples	Investigator
Gastric residual volume (>300mls)	Electronic/paper clinical records	Investigator
Diarrhoea	Electronic/paper clinical records	Investigator
Vomiting	Electronic/paper clinical records	Investigator
Pro-kinetic use	Electronic/paper clinical records	Investigator
Discharge location	Electronic/paper clinical records	Investigator
Sit-to-Stand Test post-ICU	Bedside assessment	ICU nurse
Bed-to Chair transfer post-ICU	Bedside assessment	ICU nurse
6-Minute Walk Test	Ward assessment	Physiotherapist
Short Physical Performance Battery	Ward assessment	Physiotherapist
Health-Related Quality of Life	Ward assessment /SF-36 questionnaire (telephone)	Investigator
Primary health care usage/costs	Electronic medical records	Investigator

Table 1: Secondary endpoints and methods of assessment. ICU=intensive care unit.

	All n=121	Intermittent feeding (n=62)	Continuous feeding (n=59)	p
Age, y	57.7 (54.7-60.6)	55.2 (51.0-59.3)	60.3 (56.0-64.1)	0.086
Male, No. (%) ¥	81 (66.9)	41 (66.1)	40 (67.8)	0.997
LOS prior to ICU Admission, d #	0.0 (0-15)	0.0 (0-15)	0.0 (0-15)	0.259
Period ventilated, d #	7.3 (0.5-48)	9.5 (0.5-48)	6.0 (0.63-43)	0.249
ICU LOS, d#	13.0 (0.7-93)	13.0 (0.7-93)	12.0 (1.5-52)	0.626
Hospital LOS, d#	22.8 (1.5-183)	22.0 (1.7-183)	26.0 (1.5-102)	0.907
APACHE II score	21.8 (19.9-23.6)	23.1 (19.9-26.2)	20.2 (18.2-22.3)	0.134
SOFA score on admission	10.4 (9.7-11.0)	10.3 (9.4-11.2)	10.6 (9.6-11.5)	0.709
ICU Survival, No. (%) ¥	87.0 (71.9)	44.0 (71.0)	43.0 (72.9)	0.173
Hospital Survival, No. (%) ¥	79.0 (66.4)	39.0 (63.9)	40.0 (69.0)	0.571
RRT, No. (%)	43.0 (36.8)	25.0 (41.7)	18.0 (31.6)	0.338
NMBA use, d#	0.0 (0-9)	1.0 (0-9)	0.0 (0-7)	0.109
Hydrocortisone dose, mg $ # Day 1	0.0 (0-800)	0.0 (0-800)	0.0 (0-800)	0.240
Hydrocortisone dose, mg Total by day 10	0.0 (0-25000)	0.0 (0-8120)	0.0 (0-25000)	0.149
Statin use, No. (%)	1 (0.01)	0.0 (0)	1.0 (0.02)	0.495

Gastro-protection, d[#]	9.5 (0-11)	10.0 (1-11)	8.0 (0-11)	0.569
Vasopressors support, d[#]	4.0(0-22)	4.0 (0-11)	4.0 (0-22)	0.962
Sedation use, d[#]	6.0(0-11)	7.0 (0-11)	5.0 (0-11)	0.279
Total propofol dose by day 10, g	10.6(3.9-10.6)	11.3(3.8-14.2)	9.9 (3.6-9.9)	0.377
Admission diagnosis, No. (%)				
Sepsis	47 (38.8)	21 (33.9)	26 (44.1)	
Cardiogenic shock	27 (22.3)	16 (25.8)	11 (18.6)	
Trauma	14 (11.6)	6 (9.7)	8 (13.6)	
Respiratory failure	9 (7.4)	6 (9.7)	3 (5.1)	
Intracranial haemorrhage	6 (5.0)	3 (4.8)	3 (5.1)	
Acute liver failure	5 (4.1)	2 (3.2)	3 (5.1)	
Acute Kidney Injury	4 (3.3)	3 (4.8)	1 (1.7)	
Drug overdose	4 (3.3)	3 (4.8)	1 (1.7)	
Emergency Surgery	3 (2.5)	1 (1.6)	2 (3.4)	
Cerebrovascular Accident	2 (1.7)	1 (1.6)	1 (1.7)	
Comorbidities, No. (%)				
Hypertension	44 (36.4)	24 (38.7)	20 (33.9)	
Chronic Respiratory Diseases	39 (32.2)	23 (37.1)	16 (27.1)	
Diabetes Mellitus	32 (26.4)	20 (32.2)	12 (20.3)	

Ischemic heart disease	18 (14.9)	11 (17.7)	7 (11.9)
Psychiatric diseases	23 (19.0)	12 (19.4)	11 (18.6)
Renal impairment	8 (6.6)	2 (3.2)	6 (10.2)
Obesity	10 (8.3)	6 (9.7)	4 (6.8)
Liver cirrhosis	9 (7.4)	3 (4.8)	6 (10.2)
Haem-oncological disease	9 (7.4)	6 (9.7)	3 (5.1)
Thyroid disease	5 (4.1)	3 (4.8)	2 (3.4)
Crohns disease	3 (2.5)	2 (3.2)	1 (1.7)
Previous CVA	2 (1.7)	1 (1.6)	1 (1.7)
Chronic pancreatitis	1 (0.8)	1 (1.6)	0 (0.0)

Table 2: Patient characteristics and demographics. ICU=Intensive Care Unit, APACHE II=Acute Physiology and Chronic Health Evaluation score, SOFA=Sequential Organ Failure Assessment Score, y=year, d=day, No.=number, LOS=Length of Stay, RRT=Renal Replacement Therapy, NMBA=Neuromuscular Blockade Agent, CVA=Cerebrovascular Accident, $=Corticosteroid dosing as hydrocortisone equivalents. Data are mean (95% confidence intervals), except for # indicating median with range. Student's T-test was used except for ¥ (Chi-squared) and # (Mann Whitney U).

Figure legends

Figure 1: CONSORT flowchart.

Figure 2: Loss of muscle mass over 10 trial days in patients randomized to continuous or intermittent feeding. Data are mean with 95% Confidence Intervals. Patient numbers are shown for trial days 1, 7, and 10 post-Randomization . Patient numbers on specific trial days are shown below figure.

Figure 3: Cumulative nutritional delivery. Panel A = Cumulative protein delivery in intermittent (n=441 days of feeding prescribed) and continuous (n=413 days of feeding prescribed) feeding arms. Panel B= Cumulative energy delivery in the same cohort. OR=Odds ratio of achieving nutritional target. Red bars represent intermittent feeding regimen, Blue bars represent continuous feeding regimen. *** Indicate $p<0.001$; **indicate $p<0.01$.

Figure 4ABCDEF: Leucine concentration curve over the 4-hour sampling period on trial day 1(A), day 7(B) and day 10(C). (D) Glucose variability over the 10-day time frame. (E) Number of hyperglycaemic days. (F) Daily insulin doses. Dashed lines represent intermittent feeding cohort, and full lines continuous feeding cohort. * represents $p<0.05$.