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PLUS

POTENTIAL NUTRITIONAL STRATEGIES TO REDUCE MUSCLE WASTING IN EARLY CRITICAL ILLNESS

Danielle E. Bear
Principal Critical Care Dietitian &
Health Education England / National Institute for Health Research Clinical Doctoral Fellow
Department of Nutrition & Dietetics
Department of Critical Care
Guy's and St Thomas' NHS Foundation Trust
London, UK

Danielle.Bear@gstt.nhs.uk

@danni_dietitian

Zudin Puthucheary
Consultant in Critical Care Medicine
Honorary Senior Lecturer
Institute of Sport Exercise Health
Division of Critical Care
University College London Hospitals
London, UK

zudin.puthucheary.09@ucl.ac.uk

This review will briefly discuss the potential role of nutrition and the schedule of delivery on reducing skeletal muscle wasting in early critical illness.

Increasing numbers of patients are surviving critical illness due to treatment advances in the early management of acutely unwell patients. This survival advantage is reflected as an increase in the number of patients experiencing long-term functional disability post-critical illness (Cheung et al. 2006; Herridge et al. 2011; Hopkins et al. 2005; Iwashyna et al. 2010;), resulting in a higher frequency of discharges from hospital to rehabilitation facilities (Kaukonen et al. 2014).

Skeletal muscle weakness, termed ICU-acquired weakness (ICU-AW), contributes significantly to the physical and functional disability observed in these patients. This has been highlighted in the recent American Thoracic Society Consensus Statement (Fan et al. 2014), and skeletal muscle wasting has been identified as a contributing factor to ICU-AW (Puthucheary et al. 2010).

Interventions to reduce skeletal muscle wasting in critical illness are therefore urgently required and have been highlighted as recent research priorities in the United Kingdom (Reay et al. 2014).

Skeletal Muscle Wasting in Critical Illness

Although the pathogenesis remains poorly understood, translational data is emerging that has defined the trajectory of skeletal muscle wasting during the first week of critical illness. The MUSCLE-UK group has shown that muscle wasting occurs early and rapidly during the first week of critical illness, and is more severe in patients with multi-organ failure (Puthucheary et al. 2013). This study used muscle ultrasound of the rectus femoris cross-sectional area along with fibre cross-section from biopsies of the vastus lateralis muscle to confirm these findings. Furthermore, using leg protein turnover, they demonstrated that patients remain in a net catabolic balance at the end of the first week of critical illness as a consequence of persistently high levels of muscle protein breakdown and decreased muscle protein synthesis.

Potential Interventions

In health, skeletal muscle is maintained by a balance of muscle protein synthesis (MPS) and muscle protein breakdown (MPB). Any prolonged change in this balance will result in an increase or decrease in skeletal muscle (Morton et al. 2015). Resistance exercise is the most potent anabolic stimulus, including during bed rest (Ferrando et al. 1997; Fitts et al. 2007), and the dose, source and timing of protein ingestion can further influence gains in skeletal muscle in those undertaking this type of exercise (Atherton et al 2010; Bohe et al. 2001; Bohe et al. 2003).

It has been assumed that similar strategies may prove useful in the critically ill. However, resistance exercise is often not feasible in the early stages of critical illness due to the clinical instability of the patient. Additionally, there are no proven nutritional therapies to attenuate skeletal muscle wasting in the ICU and translational science in this area is severely lacking (Bear et al. 2013). When considering nutritional strategies to reduce muscle wasting in the critically ill, one must consider the timing, route of delivery and the amount of nutrient required to elicit a benefit. Each of these factors remains under debate for almost all areas of critical care nutrition.

Protein

Protein is the most obvious potential nutrient to reduce muscle wasting in this population, but data indicating a clear benefit to higher protein levels are lacking. Indeed a systematic review of protein provision in critical illness detailed the limited amount and poor quality of the available evidence and highlighted several shortcomings of studies investigating protein intakes in critically ill patients (Hoffer and Bistrian 2012).

The majority of randomised controlled trials (RCTs) investigating protein intake in critical illness were undertaken before 2000 (Greig et al. 1987; Iapichino et al. 1988; Ishibashi et al. 1998; Larsson et al. 1990; Long et al. 1976; Muller et al. 1995; Pitkanen et al. 1991; Shaw et al. 1987; Twyman et al. 1985; Wolfe et al. 1983), with very few undertaken after that time (Scheinkestel et al. 2003a; Scheinkestel et al. 2003b; Singer et al. 2007; Verbruggen et al. 2011). Protein doses of up to 3.5g/kg were studied and nearly all of these used parenteral amino acids and reported nitrogen balance as the primary determinant of benefit from higher protein intakes. Notwithstanding the limitations of small sample size, the method of using whole body nitrogen balance is often flawed in the critically unwell due to the failure to account for losses in skin and faeces (Kopple 1987). Additionally, this method is not reflective of muscle mass, as the gastrointestinal and liver contributions remain unknown and are potentially high (Guillet et al. 2004). Whilst two studies measured protein turnover (Wolfe et al. 1983; Verbruggen et al. 2011), this was in fact whole body turnover, which also does not reflect muscle turnover itself.

Despite the lack of data from RCTs, current recommendations in the critically ill are for higher protein intakes ranging from 1.5-2.5g/kg/day (Hoffer and Bistrian 2012; Kreymann et al. 2006; McClave et al. 2016). These recommendations are based mainly on observational data and relate to a mortality benefit (Alberda et al. 2009; Allingstrup et al. 2012; Elke et al. 2014; Weijs et al. 2012; Weijs et al. 2014) rather than a reduction in the loss of lean body mass itself.

Only one study has investigated the effect of different protein intakes on patient-centred outcomes, including muscle wasting, in the critically ill. In the study by Ferrie and colleagues (2015), 119 patients were randomised to receive 0.8g/kg or 1.2g/kg protein from parenteral nutrition (PN). Despite a smaller than planned difference in the delivery of protein (0.9g/kg vs 1.1g/kg), they found a significant difference in the primary outcome of handgrip strength at day 7 along with improvements in secondary outcomes such as fatigue score and measures of forearm muscle thickness and rectus femoris cross-sectional area. These results indicate that higher protein intakes, at least when supplied via the parenteral route, may lead to reductions in muscle wasting during the first week of critical illness. However, this finding needs to be confirmed in larger studies, correcting for baseline heterogeneity, especially as these results are in stark contrast to observational data reported from two groups.

In two pre-planned sub-studies from the large EPaNIC Trial, early parenteral nutrition (PN) (and therefore higher provision of protein) was not found to reduce muscle wasting (Casaer et al. 2013; Hermans et al. 2013). In the first of these (Hermans et al. 2013), muscle atrophy, measured using muscle biopsies, was not different between the groups receiving early or late PN. In the second, repeated femoral and abdominal CT scans were obtained in 15 neurosurgical patients. Whilst early PN was shown to reduce the quality of the muscle, it did not affect the rates of wasting seen in this group of patients.

Puthucheary et al. (2013) used muscle ultrasound of the rectus femoris cross-sectional area to inform the trajectory of muscle wasting over a 10-day ICU stay in 63 patients. Muscle loss in this group was early and rapid, with patients losing on average 17% of their lean body mass over this time period. Additionally, patients with multi-organ failure experienced significantly more muscle loss than those patients with single organ failure (21.5% vs. 7.2%). This finding was confirmed by the data from muscle biopsies of the vastus lateralis. Protein tracer studies indicated that the muscle loss was due to increased protein catabolism and reduced protein synthesis over the first 7 days; however, muscle loss in this group was also found to be positively associated with protein intake over the study period.

> **“ simply reducing the macronutrient deficit over the first week of critical illness may not be a useful strategy for reducing muscle loss ”**

These studies indicate that simply reducing the macronutrient deficit over the first week of critical illness may not be a useful strategy for reducing muscle loss. It is likely that any nutrition intervention aimed at reducing muscle wasting will need to consider the delicate relationship between both energy and protein provision. Energy intake is a fundamental requirement for utilisation of amino acids and protein (Burke 2010; Calloway 1955; Kreymann et al. 2012). However, current trends are towards lower energy intakes in the first week of critical illness due to the potential for harm seen with aggressive early energy provision (Braunschweig et al. 2015; Casaer et al. 2011). Further, interventional trials increasing delivery of protein and calories will need to be designed with caution and consider the physiological mechanisms behind such strategies.

Feeding Schedule

The contradictory results and current controversies rest on the assumption that our current modes of delivery are best. A recent large study found no difference in mortality (30- or 90-day) or infectious complications when early PN was compared with early enteral nutrition (EN) (Harvey et al. 2014). Considering its non-nutritional benefits (McClave et al. 2014), EN remains the route of choice in early critical illness (McClave et al. 2016), despite the large degree of underfeeding associated with its use (Alberda et al. 2009). However, more fundamental to the route and volume of nutrition support is that each nutritional component needs to be delivered to the plasma from the gastrointestinal tract and then transported into cells to be utilised by the muscle. Gastrointestinal intolerance is common in critically ill patients, especially in terms of delayed gastric emptying (Nguyen et al. 2007). It has been shown that these patients experience impairments in both the rate and extent of nutrient absorption, even when post-pyloric feeding is utilised (Di Bartolomeo et al. 2012), which may confound any potential to see a positive impact of nutrition in preventing muscle wasting.

Additionally, it is possible that our current methods of continuous feeding may not be appropriate as a result of the muscle full effect. The concept of the muscle full effect has been studied in small groups of healthy individuals, where it has been found that upon ingestion of either whey protein (45g; Atherton et al. 2010) or commencement of intravenous amino acids (Bohe et al. 2001), a latent period of around 30-45 minutes exists where MPS then triples for up to 90 minutes before rapidly returning to post-absorptive rates. This reduction back to baseline MPS occurs despite continued availability of essential amino acids both intramuscularly and in the plasma. Additional amino acids were oxidised in both groups. These results indicate that, irrespective of the route of feeding, a simple overprovision of amino acids does not lead to continued increases in MPS. Although the muscle full effect has not been studied directly in critically ill patients, in a small group of critically ill patients studied over a 3-hour period, whole body protein balance was shown to increase due to synthesis, and amino acids were not oxidised at the equivalent of 1g/kg/day, indicating that amino acids at this level at least are utilised in these patients (Liebau et al. 2015). However, any direct relationship to muscle protein synthesis cannot be inferred due to the use of the whole body protein turnover method whereby hepatic oxidation may fully account for these findings.

These data together suggest that continuous feeding may not allow physiological stimulation of intermittent MPS and that intermittent (bolus) feeding may be better (Atherton et al. 2010; Marik 2015). Intermittent feeding has been previously investigated in critical illness (Evans et al. 2016; MacLeod et al. 2007), but muscle mass and function were not measured. The Muscle-UK group is currently investigating the effect of this feeding schedule on changes in the rectus femoris cross-sectional area with results expected in 2017 (**Intermittent Versus Continuous Feeding in ICU Patients,** NCT02358512 **clinicaltrials.gov/ct2/show/NCT02358512**).

This review has not addressed specific amino acids (e.g. leucine), their metabolites (eg. ß-hydroxy-ß-methylbutyrate) or the post-ICU phase of critical illness. Discussions on these are beyond the scope of this article, but future studies may be aimed not at the acute phase, but in trying to rebuild the lost muscle. It is most likely that nutritional interventions are only one of several aspects needed for the increase in muscle mass and strength in the post-ICU phase and that when coupled with exercise, stronger benefits may be produced (Heyland et al. 2015).

Conclusion

Reducing muscle wasting and subsequent ICU-AW to improve the function and quality of life of ICU survivors are high priorities for critical care clinicians. No known intervention exists to achieve this at present, but several nutritional interventions may prove successful such as appropriate protein and energy provision and intermittent feeding. However, further translational science work, along with investigations into the patient group most likely to benefit are required before these interventions can be confirmed in large RCTs.

Conflict of Interest

Danielle Bear declares that she has no conflict of interest. Zudin Puthucheary declares that he has no conflict of interest. ■

Abbreviations

EN enteral nutrition
ICU intensive care unit
ICU-AW ICU-acquired weakness
MPB muscle protein breakdown
MPS muscle protein synthesis
PN parenteral nutrition

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