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Systematic Review

Pharmacotherapies for muscle wasting in older ICU patients: A narrative review of the current literature

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160 Character summary: This article was written as my MD research project, in my 3rd year of medical school during the latter half of 2020. It focuses on the current drugs available to combat the deadly intersection of frailty with critical illness, a combination which often results in frail patients experiencing worse outcomes upon becoming critically ill. Poorer outcomes in this cohort of patients are due in large part to muscle wasting, which is a significant component of both critical illness and frailty in isolation. Thus, when frailty and critical illness combine, muscle wasting is amplified, and this leads to significant morbidity. Due to the limited range of therapeutic delivery modalities in the ICU, adequate pharmacotherapy would be a convenient method of managing this dilemma. The purpose of this article was to review pharmacotherapies that have been tested in this distinct population.

Key words*:* Critical illness, ICU, Frailty, Sarcopenia, Muscle Wasting

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Three learning points:

1. At present, there is no easy fix for muscle wasting in critical illness. The need for an effective and safe therapy targeting this important issue remains unmet.

2. Mitigating the amount of muscle we lose with age, via appropriate physical activity and nutrition throughout life, is perhaps one of the few physiological defenses we have for periods of critical illness in older age.

3. For the future of therapies targeted at reducing muscle loss in critical illness, the most promising research currently lies in biologic therapies.

ABSTRACT

Background: The predominantly geriatric syndrome of frailty can result from the gradual reduction of function in multiple physiologic systems that occurs with increasing age. Critical illness accelerates the age-related loss of muscle that often accompanies frailty, and the combination of these two conditions creates a distinctly morbid state of vulnerability. Muscle wasting while in the intensive care unit (ICU) results in greater patient morbidity, making the preservation of muscle mass an important therapeutic target. This article narratively reviews the drug therapies that have been trialed for mitigating muscle wasting in older critically ill patients.

Materials and Methods: MEDLINE, PubMed, Web of Science and EMBASE were searched. Inclusion criteria were drug trials with muscle-related outcome measures in critically ill populations aged 50 or older. Exclusion criteria were non-pharmacological interventions, a lack of muscle related outcomes, review articles, case studies, case series and non-English articles.

Results: From 4586 identified articles, 27 articles were included in the final review. While burn populations benefitted from oxandrolone, the only pharmacotherapy that demonstrated an improvement of muscle outcomes in older general ICU patients was intensive insulin therapy. However, due to the risk of hypoglycaemia, the use of intensive insulin therapy remains largely unfavourable.

Discussion: The requirement for an effective drug therapy targeting the preservation of muscle mass in older ICU populations remains unfulfilled. Several novel drug therapies targeting myostatin and activin receptors have recently been studied in frail, non-critically ill populations. Future research should focus on studying novel pharmacotherapies in the frail and critically ill.

Introduction

Muscle loss is a core feature of both critical illness and frailty. Patients with a combination of these two catabolic states have a heightened risk of morbidity and mortality, proportional to the amount of lean body mass that is lost [1, 2]. Frailty, which increases with age, is defined as a state where the generalised impairment of multiple organ systems results in an increased vulnerability to stressors. A condition related and often comorbid to frailty is sarcopenia, which is the progressive age-related loss of skeletal muscle mass and strength [3-5]. The chronic catabolic state of frailty is partly due to inflammatory mediators that are also elevated in critical illness [3]. Previous studies have demonstrated that approximately one in three patients admitted to ICUs are frail, and frailty is associated with an increased incidence of critical illness [3, 6, 7]. When the frail with pre-existing sarcopenic muscle loss are afflicted by critical illness, the combination of these two conditions leads to an amplification of lean mass loss and a rise in morbidity [1].

Critical illness encompasses life-threatening disorders of the respiratory, cardiovascular or neurological systems, often in combination. Regardless of the primary cause of disease, critical illness is accompanied by muscle loss, including loss of respiratory muscle, beginning in the acute phase of severe disease [8, 9]. This is due to a dramatic hypermetabolic response that results in profound proteolysis, as metabolic derangement results in protein being used more for energy rather than for protein synthesis [1, 10-12]. With muscle being the largest protein reservoir in the body, muscle is broken down for fuel. This catabolic response is a prolonged process which has severe implications for long-term prognosis and recovery. The loss of muscle mass leads to decreased strength, causing a markedly impaired capacity for rehabilitation [8, 11, 13]. More than half of ICU survivors have been shown to experience a substantially reduced quality of life, financial hardship and significant loss of function enduring long after their ICU admission [14, 15].

In the critically ill, the preservation of lean body mass and skeletal muscle function is vital not only for reducing the acute risk of morbidity and mortality, but also in achieving satisfactory post-ICU outcomes. Neither nutritional nor physical therapies in isolation adequately address the loss of muscle in ICU, and, thus, alternative interventions are required [7, 14, 16-20]. Pharmacological therapies are an attractive option. The purpose of this review was to identify and evaluate all of the pharmacological therapies that have been used to mitigate muscle wasting in older ICU patients.

Materials and Methods

On the 04/09/2020, a search was conducted on MEDLINE, PubMed, Web of Science and EMBASE, using the following search strategy: ("Intensive Care" OR "Critical Care" OR "Critical Illness") AND (Frail* OR Sarcopeni* OR "Weakness") AND (therap* OR "Pharmacotherapy"). No restrictions were placed on the search. Reference lists of each included study were screened for relevant articles which had not been included in the initial search. Included studies had populations of critically ill adults with an average age of 50 or older. This minimum average age was set to capture a frailer cohort, as older adult populations would be more likely to have a higher prevalence of frailty, and literature specific to frail populations was limited. Study interventions must have included a pharmacotherapy and reported outcomes on a muscle-related measure, including measures of protein balance and metabolism and measures of muscle function, such as the duration of ventilatory support. Exclusion criteria included non-pharmacological interventions or studies without muscle-relevant outcomes. In addition, non-critically ill surgical populations, review articles, case studies, case series and studies not available in English were excluded.

Results

Following the removal of duplicate publications, the initial search identified 4586 articles, including 42 from the reference lists of included studies (Figure 1). 4477 articles were excluded after title and abstract screening, and 82 were excluded following full-text review, leaving 27 articles meeting inclusion criteria. No studies utilising novel biologic therapies were identified. There were eight publications on recombinant human growth hormone (Table 1) (8-11, 21-24), fourteen on insulin therapy (Table 2) (25-38), two on oxandrolone, (Table 3) [39, 40], one on intravenous immunoglobulin (Table 4) [41], and two investigated theophylline for the diaphragm (Table 5) [42, 43].

Growth hormone

Each of the eight studies investigating the impact of recombinant human growth hormone (rHGH) injections in older critically ill patients measured markers of protein metabolism [8-11, 21-24]. In the first of these, patients lost significantly less protein following four days of rHGH, but, nonetheless, remained catabolic overall [21]. Similarly, a subsequent study showed increased protein synthesis with rHGH, but apart from a transient anabolic period in a small population subset, patients were largely catabolic [23]. However, two trials of rHGH induced enough protein synthesis to attain a positive protein balance, which was a marked improvement relative to controls in both settings [9, 11]. A further three studies that measured nitrogen balance, a surrogate for protein metabolism as nitrogen retention corresponds with protein retention, demonstrated significant but transient improvements with rHGH [10, 22, 24, 44].

Two of the rHGH studies measured muscle function [22, 24]. The first, a trial of 20 patients on prolonged mechanical ventilation, reported a significant improvement in lean body mass, accompanied by a marked improvement in nitrogen balance, with rHGH [22]. However, these improvements did not influence mechanical ventilation duration, nor did they affect muscle strength. The second study, a large multicentered trial in frail ICU patients requiring prolonged admission, also could not demonstrate a benefit [24]. In fact, rHGH significantly increased the duration of mechanical ventilation and impaired exercise tolerance [24].

Intensive insulin therapy

Trials of intensive insulin therapy (IIT) commonly included the duration of mechanical ventilation as an outcome measure, and several large studies reported that IIT could expedite weaning. In the first major study of IIT in 1548 patients, Van den Berghe and colleagues [25] initially did not demonstrate an effect on the duration of ventilatory support. However, this overall population had a two-day median requirement of ventilatory support, and subgroup analyses in those with ICU admissions longer than five and 14 days showed that IIT did, in fact, reduce their duration of ventilatory support significantly. Similar results were found in a later study by the same group, and while the IIT population overall had reduced weaning time (Hazard Ratio 1.21, 95% CI 1.02-1.44), those requiring admission for longer than three days had a greater benefit from tight glycaemic control (Hazard Ratio 1.43, 95% CI 1.16-1.75) [27]. In those admitted to ICU for a week or more, IIT was later found to be independently protective against prolonged mechanical ventilation (Odds Ratio 0.56, 95% CI 0.36-0.87) [28]. A separate research

group also demonstrated that IIT reduced ventilation time by nearly two days (Median 4.2 days vs. 6.1 days) in 483 postoperative brain surgery patients requiring three or more days of admission [35].

Overall, however, more studies found evidence that IIT did not improve the duration of mechanical ventilation. The largest IIT trial was conducted by the NICE-SUGAR Study investigators in 6104 patients expected to have ICU admissions of at least three days. With IIT, maintaining euglycaemia between 4.5-6.0 mmol/L provided no weaning benefit [33]. Both the IIT and control populations required an average of 6.6 days of mechanical ventilation. These results were in concordance with three large, earlier studies which showed no weaning benefit from tight glucose control below 6.1 mmol/L [30-32]. Three later trials also failed to show any improvement of mechanical ventilation with IIT [34, 36, 37].

Three studies explored the impact of IIT on critical illness polyneuropathy (CIP). Compared to conventional glycaemic control, IIT-treated patients in the first Van den Berghe trial [25] were less likely to have CIP when screened. Conventional insulin therapy was found to be an independent predictor of CIP (OR 2.6, 95% CI 1.6-4.2). In their later trial, critical illness neuromyopathy (CINM) incidence was significantly lower in patients receiving IIT, and IIT was an independent protective factor for CINM (OR 0.61, 95% CI 0.43-0.92) [28]. The most recent study of insulin therapy in frail ICU patients reproduced these results with a less restrictive blood glucose range of 4.4-7.8 mmol/L [38].

Oxandrolone

Demling et al. conducted two studies investigating the effect of oxandrolone on muscle in older patients with major burns, and both studies demonstrated significant benefit [39, 40]. The first administered oxandrolone during rehabilitation and resulted in a higher weekly weight gain than controls. Further, 76% of this weight gain was lean mass, which was significantly higher than the 51% gained in the control patients. This translated into an improved Functional Independence Measurement score at discharge from rehabilitation [39]. A subsequent study by the same group administered oxandrolone prior to rehabilitation in 50 acute post-burn patients and demonstrated a significant protein-sparing effect, as well as a significant preservation of body weight and a reduced time to discharge.

Intravenous immunoglobulin

Brunner et al. [41] are the only research group that investigated intravenous immunoglobulin (IVIG) in older critically ill patients. IVIG was trialed in 38 septic patients but failed to improve either CIP or critical illness myopathy (CIM), and the apparent futile effect of IVIG led to the early termination of the study [41].

Theophylline

Two recent studies investigated theophylline for assisting older ICU patients to wean from mechanical ventilation. The first study demonstrated that theophylline exerted a marked improvement in diaphragm movement by increasing diaphragmatic excursion in mechanically ventilated patients. However, these patients did not wean faster than

controls, and had no significant reduction in ventilator time [42]. The results were similar in a subsequent study conducted in 160 comparable patients. Theophylline provided a significant improvement in global tests of respiratory muscle strength, however, did not significantly improve weaning success or reduce mechanical ventilation time [43].

Discussion

For the older general ICU population, IIT was the only therapy that demonstrated an improvement in muscle outcomes. However, due to the risk of hypoglycaemia with IIT its use remains controversial. No clinical benefit could be demonstrated by rHGH, IVIG or theophylline. While oxandrolone was beneficial for older patients with burns, it was not studied in a general ICU cohort. Muscle wasting derived from increased protein breakdown and decreased protein synthesis are core features of both frailty and critical illness, making protein metabolism a major therapeutic target [2]. Studies have largely focused their efforts on countering this net catabolism with the anabolic hormones insulin and growth hormone, which are depleted in illness and advancing age, and share similar anabolic mechanisms [1].

1. *Growth Hormone*

Growth hormone (GH) exerts a potently anabolic effect by increasing the cellular influx of amino acids, while also decreasing amino acid efflux, which enhances cellular proliferation and protein synthesis [60, 61]. Moreover, GH increases fat oxidation, which reduces the amount of protein being used for energy and, thus, further increases the amount of protein substrate available for protein synthesis [1]. GH production declines rapidly following young adulthood, and is released in even smaller quantities during prolonged ICU admission [7]. Thus, replenishing its levels in the old and critically ill seems a plausible strategy for countering catabolism [1].

Despite rHGH consistently producing an anabolic effect by improving protein balance, even leading to an increased muscle mass, it failed to have an impact on clinical outcomes. Indeed, two studies which enhanced nitrogen balance, yet failed to achieve functional improvement, cast doubt on the utility of using protein metabolism markers to make inferences on muscle function [22, 24]. Apart from most studies not reporting on functional outcomes, a notable limitation is that all but one study had small sample sizes of between 11 to 21 patients.

The single large, multicentered growth hormone study produced concerning results, with rHGH causing a significantly increased duration of mechanical ventilation, and a marked impairment of exercise tolerance [24]. Furthermore, rHGH administration also increased mortality (42% versus 18% in controls). These results were unexpected, and it was later suggested that excessive doses of rHGH may have been the cause [45]. The high doses used led to a subsequent increase in IGF-1 levels which likely caused several unintended effects, including hypercalcaemia, fluid retention and insulin resistance with accompanying hyperglycaemia [45]. The harm caused by over-supplementation of GH suggests that the suppression of its release in response to critical illness may be appropriate in some capacity [7].

The clinical utility of GH, as used in these older studies, appears limited, and in recent years, there has been minimal research of growth hormone supplementation in frail critically ill populations. However, if GH were to be further investigated, it has been suggested that studies attempt to attain lower, more pulsatile GH concentrations that better represent physiologic activity [7, 45]. This may be attainable with GH secretagogues, including GH releasing peptide-2 and thyrotropin releasing hormone [45].

2. *Insulin*

Insulin has critical anabolic actions [1]. Following protein and carbohydrate ingestion, it is the most important hormone in mediating an anabolic response [2]. Insulin enhances amino acid uptake in cells, increases the synthesis of fatty acids and decreases protein catabolism [46, 47]. However, in critical illness, the anabolic effect of insulin is dampened by the hypermetabolic response induced by catabolic factors, including cortisol, inflammatory cytokines and catecholamines [12, 48]. Furthermore, this hypermetabolic response also induces insulin resistance, and the resulting hyperglycaemia is a risk factor for ICU-acquired weakness [12, 49]. Thus, the two-pronged impairment of the functions of insulin impacting muscle during critical illness have made insulin therapy the most popular as per the literature.

Several studies are ultimately divided on the impact of IIT for weaning from mechanical ventilation in older ICU patients, with three large trials suggesting a benefit particularly for those with longer admissions [25, 27, 28, 35], while seven other trials failed to demonstrate any benefit [30-34, 36, 37]. This discordance of results is likely partly accounted for by marked differences in the studies. These include differing study protocols, populations, differing times of glucose control initiation and differences in the realized levels of glucose control [50] Schultz et al [50] provide a comprehensive discussion surrounding the discrepancies of these trials.

CIP was reduced by IIT in three trials [25, 28, 38]. Intensive care unit acquired weakness (ICUAW) is the main clinical manifestation of CIP, CIM, or the combination of CIP and CIM known as CINM [51, 52]. ICUAW presents as a generalised muscular weakness and occurs in up to 50% of ICU patients, frequently resulting in a prolonging of mechanical ventilation, and is associated with increased mortality and long-term disability [51-54]. The positive results of these trials indicate that avoiding hyperglycaemia with insulin therapy is likely beneficial for patients at risk of developing CINM, and, thus, ICUAW [51].

Ultimately, glucose control remains a significant therapeutic target in older ICU patients, but due to discordant results from studies, the ideal range and method of control continue to be elusive [50]. Additionally, it is important to consider the higher incidence of hypoglycaemic episodes with intensive glucose control, and while not leading to morbidity in most cases, it was associated with increased mortality in the NICE-SUGAR Study [33]. Due to the divided results from many large trials, it is clear that more evidence is needed before a recommendation can be made regarding appropriate glycaemic control in older critically ill populations.

3. *Oxandrolone*

Oxandrolone acts through the same mechanisms as testosterone to maximize its anabolic action, but with fewer masculinizing effects [1]. By stimulating androgen receptors, it acts similarly to growth hormone and insulin by increasing the amount of amino acids in cells. Indeed, protein synthesis is induced, new tissue is generated and fat becomes the preferred source of energy [1]. Burns are a particularly catabolic subset of critical illness

with marked muscle breakdown and are thus an especially troublesome complication for older patients with pre-existing muscle loss [39, 55].

Both studies of oxandrolone in older burn patients produced positive results. The first study was limited by a small sample size of 15, but the same research group's later study in a larger population of 50 patients reproduced its positive results. In the later study, as patients' discharge relied on functional ability, the authors concluded that the reduced discharge time likely reflected preservation of muscle mass [40]. Thus, both studies successfully demonstrated that oxandrolone's body weight-preserving effect could be translated into palpable clinical benefits.

The promising results of oxandrolone in burn patients have resulted in its regular use in this population [14]. A meta-analysis of oxandrolone in patients with severe burns shows findings in other burn populations consistent with those of Demling's trials [56]. Unfortunately, there has been no research on oxandrolone in older non-burn ICU populations, which limits the external validity of the effectiveness of oxandrolone.

4. *Intravenous immunoglobulin*

Due to the strong association of CINM with sepsis and systemic inflammation, it was thought that the administration of IgM-enriched intravenous immunoglobulin (IVIG) could mitigate the effects of CIP and CIM. In a single study, IVIG was theorized to modulate pro-inflammatory cytokines, thereby reducing cytokine-mediated neuron and muscle protein damage [41]. However, the results of the study [41] were ultimately disappointing as IVIG showed no improvement of either CIP or CIM, and the trial concluded early as a result. The effect of IVIG on muscle in the frail and critically ill is limited to the results of this single small trial, which suggest a lack of benefit.

5. *Theophylline*

Prolonged mechanical ventilation results in respiratory muscle weakness, due to diaphragmatic atrophy and contractile dysfunction. This contractile dysfunction is linked to an increase in reactive oxygen species, causing proteolysis in the diaphragm [57]. Theophylline is a methylxanthine that has demonstrated beneficial effects in various patient populations by strengthening respiratory muscles and improving diaphragm function [42]. It was hypothesized that theophylline could inhibit xanthine oxidase, a source of reactive oxygen species that increased activity in the diaphragm after prolonged mechanical ventilation in animal models [43, 57].

Neither of the theophylline studies [42, 43] could improve weaning outcomes for older critically ill patients, despite improvements to respiratory muscle function. Due to its large sample size, the later study, in particular, provides convincing data on the lack of utility for theophylline in weaning [43]. Thus, theophylline's use in this capacity cannot be currently recommended.

6. *Novel therapeutics*

The therapies outlined in this review have largely produced unsatisfactory results and new biologic drugs are currently under investigation. Particular interest has been garnered in the inhibition of activin receptors and myostatin. Bimagrumab, a monoclonal antibody against activin receptor type II, significantly improved muscle mass, strength and gait speed in sarcopenic adults [58], but a more recent trial could not reproduce functional benefit (NCT02333331). Anti-myostatin antibodies Landogrozumab (NCT01369511) and Trevogrumab (NCT01963598) have both increased lean mass in the frail, but with no functional improvements. Similarly, targeting the androgen receptor with selective androgen receptor modulators has produced lean mass gains in frail women, again without functional benefits [59]. These therapies are yet to be trialed in the critically ill.

Limitations of Included Articles

The included studies also have limitations. Many of the included trials had small samples and, in some instances, investigators were not blinded which likely introduced bias. Several studies were not randomised controlled trials. Additionally, most of the included trials are over 10 years old, further emphasising the need for future research on novel drug therapies in this field. Moreover, their frequent reporting of surrogate measures of muscle rather than clinical outcomes is a limitation, as these do not always reliably translate into clinical effects. Notably, the literature investigating muscle-related outcomes in frail critically ill populations was minimal.

Limitation of this Review

This review has some important limitations. These include there being a single reviewer, exclusion of non-English articles and no formal quality assessment of the literature. Due to the higher prevalence of frailty in older populations, any trial with an average age less than 50 was excluded to better capture a frailer cohort. As a result, frail populations younger than 50 may have been excluded, and non-frail populations 50 or older were possibly included.

Conclusions

Muscle loss in critical illness contributes to a variety of detrimental patient outcomes, with a particularly high risk conferred to those with pre-existing loss of muscle mass. Strict glucose control with insulin is the only drug therapy to have improved muscle outcomes of older patients with critical illness, but its risk of hypoglycaemia creates implications for its use. Oxandrolone has proven beneficial for older burn patients, but has not been adequately studied outside of this population. The results of this review emphasise the necessity for further research of novel experimental therapies, aimed at generating functional benefit for the frail critically ill populations who need it most.

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