Muscle Wasting & Weakness in Critical Illness

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Disclosures

• I have no disclosures in respect of this presentation
Clinical review: intensive care unit acquired weakness

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Abstract

A substantial number of patients admitted to the ICU because of an acute illness, complicated surgery, severe trauma, or burn injury will develop a de novo form of muscle weakness during the ICU stay that is referred to as "intensive care unit acquired weakness" (ICUAW). This ICUAW evoked by critical illness can be due to axonal
ICU acquired weakness

• Generalised muscle weakness developing during the course of an ICU admission for which *no other cause* can be identified besides the acute illness or it’s treatment
Skeletal muscle wasting & weakness in critical illness

- Occurs commonly
  - Particularly in mechanically ventilated patients
  - Particularly in longer-stay patients

- Is of clinical significance
  - Can dominate the long-term course of illness & impede recovery – “Post intensive care syndrome”

- Prevalence, causes, prevention & treatment remain poorly understood
Functional Disability 5 Years after Acute Respiratory Distress Syndrome

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“We found that relatively young patients who survived ARDS had persistent exercise limitations and a reduced physical quality of life 5 years after their critical illness. Pulmonary function was near-normal to normal at 5 years. The decrements in quality of life and exercise capacity may have resulted from persistent weakness,......”
Incidence

• Frequent
  – 26-65% patients ventilated 5-7 days\textsuperscript{1,2}
  – Up to 67% patients ventilated ≥10 days\textsuperscript{3}
  – In ARDS patients, 60\%\textsuperscript{4}, and still present at discharge in 36\%\textsuperscript{5}

• 3 ICUs, 5yrs, all ICU LOS >28 days
• 22/86 eligible patients studied
  – 5 unable to attend because of ill health or immobility
  – Median follow-up 43 (12-57) months
  – All admitted severe weakness & functional impairment for prolonged period following hospital discharge
• Findings:
  – Clinical motor or sensory deficits in 59%
  – EMG c/w preceding axonal neuropathy in 95%
Differential diagnosis of weakness in the ICU patient

- Weakness caused by the disease
- Acute weakness related to therapies
  - Corticosteroids
  - Sedative agents
  - Neuromuscular blocking drugs
  - Aminoglycosides
- ICU-acquired weakness
  - Weakness developing without an identified cause except non-specific inflammation
  - Essentially a bedside diagnosis
Weakness and illness

• Weakness associated with critical illness recognised for over a century
  Osler W. Principles and practice of medicine. 1892

• Loss of muscle protein occurs rapidly & approximates 2%/day
  Gamrin L et al., Metabolism 1997;46:756-62
Aetiology & Risk Factors

• Early reports implicated SIRS, sepsis & MOF
  • Considered another “Organ Dysfunction / Failure”?  
    – However, reported also in patients that had none of these...

• High incidence in asthmatics implicated certain drugs
  • Corticosteroids, Neuromuscular blocking agents
    – However, later reports confirmed high incidence in patients that never received these drugs...
“Neuromyopathy”

Stevens RD et al., Crit Care Med 2009;37:S299-S307

Figure 1. Classification of intensive care unit-acquired weakness (ICUAW). CIP, critical illness polyneuropathy; CINM, critical illness neuromyopathy; CIM, critical illness myopathy.
“Neuromyopathy”

Figure 1. Classification of intensive care unit-acquired weakness (ICUAW). CIP, critical illness polyneuropathy; CINM, critical illness neuromyopathy; CIM, critical illness myopathy.

Stevens RD et al., Crit Care Med 2009;37:S299-S307
Pathophysiology
Causes of weakness and wasting: Immobilisation

- Muscle strength declines 1% / day of strict bed rest in healthy adults
- Muscle wasting commonly accompanies disuse
- 40% loss mean muscle fibre area over 6-7 weeks in healthy young adult
  

- Limb immobilisation -> 25% decline in muscle strength in 7 days
- Wasting occurs rapidly in critical illness
- Fibre size falls within 7 days of ICU admission
Measures of muscle wasting in critical illness

- Conchotome biopsy
- Conchotome biopsy, ultrasound evaluation & Protein:DNA ratio measurement
Muscle protein turnover in sepsis

Muscle protein turnover in critical illness – human study

Puthucheary ZA et al., JAMA 2013;310:1591-600
Possible causes of protein loss

Reduced protein synthesis & increased protein breakdown...

• Inflammation
  – TNFα, IL-1, IL-6

• Immobilisation

• Endocrine stress responses

• Nutritional deficit

• Microcirculatory derangements
Causes of muscle dysfunction

• Muscle membrane inexcitability
  – Sodium channel dysfunction\(^1\)
  – Altered intracellular calcium homeostasis\(^2\)

• Muscle bioenergetic failure
  – Oxidative stress, mitochondrial dysfunction and ATP depletion\(^3\)

• ‘Denervation’ effects

1. Ackermann KA et al., Crit Care 2014;18:484
2. Zinck W et al., Crit Care Med 2008;36:1855-63
Nerve – muscle dysfunction

• Pathological finding in CIP is axonal degeneration\(^1\)
  – Pathogenesis is not completely understood
  – Implicated:
    • Microvascular changes in endoneurium evoked by sepsis\(^2\)
      – Endoneurial oedema -> impaired axonal energy delivery -> axonal death
    • Direct toxic effects of hyperglycaemia\(^3\)

2. Fenzi F et al., Acta Neuropathol (Berl) 2003;106:75-82
3. Hermans G et al., Am J Respir Crit Care Med 20007;175:480-9
Steroids and muscle relaxants

Cholesterol

Vecuronium
Steroids

• In animal models steroids cause selective muscle fiber atrophy similar to CIM
• Muscle changes worsened significantly by denervation
• Observational studies in humans conflicting:
  – 3 trials suggested steroids deleterious
  – 3 trials found no effect
  – 1 study suggested benefit!
• Low-dose steroid trials?
  – CORTICUS: No difference in incidence CINM

Sprung CL et al., NEJM 2008
Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

respectively. Methylprednisolone was associated with significantly increased 60- and 180-day mortality rates among patients enrolled at least 14 days after the onset of ARDS. Methylprednisolone increased the number of ventilator-free and shock-free days during the first 28 days in association with an improvement in oxygenation, respiratory-system compliance, and blood pressure with fewer days of vasopressor therapy. As compared with placebo, methylprednisolone did not increase the rate of infectious complications but was associated with a higher rate of neuromuscular weakness.

CONCLUSIONS
These results do not support the routine use of methylprednisolone for persistent ARDS despite the improvement in cardiopulmonary physiology. In addition, start-
Steroids and muscle relaxants

Do steroid-based NMJBs have the dual effect of steroid + denervation?

– Prolonged effect of vecuronium, pancuronium in renal failure
– Increased incidence of weakness in asthmatics requiring ventilation + NMJBs [Douglass J. Am Rev Respir Dis 1992]

• However...
  – All studies retrospective
  – Fail to control for illness severity, sepsis, hyperglycaemia, other therapies
  – Identical clinical features reported in patients NEVER receiving NMJBs
  – Recent ARDS trial found benefit from steroid therapy on survival & reduced ventilator days without increase in weakness (cisatracurium) [Papazian L et al., N Engl J Med 2010]
ICU-acquired weakness: Clinical features

• Assessment often confounded by effects of:
  – Illness (encephalopathy)
  – Sedation
  – Delirium
• Classically symmetrical flaccid motor deficit
  – Paresis -> Quadriplegia
• Sensation usually preserved
• Cranial nerves often spared
• Reflexes classically depressed or absent
  (but normal reflexes not uncommon)
Critical illness polyneuropathy

- Distal axonal sensory-motor polyneuropathy
- Limb & respiratory muscles
- Facial muscles spared
- Lower > Upper limbs, Distal > Proximal
- Often preceded by encephalopathy (?septic)
- Frequent presentation with difficulty weaning or obvious weakness
Nerve conduction in CIP

- Reduced amplitude CMAPs & SNAPs with normal or mildly reduced nerve conduction velocity
- Varying degrees of fibrillation potentials & positive sharp waves
- Absent, normal, or myopathic motor unit potentials (?overlap CIP/CIM)
- Primary axonal degeneration, denervation atrophy of muscle on histology
Prognosis

• Prolonged ICU & hospital stay, prolonged duration of mechanical ventilation, increased ICU & hospital mortality

• Recovery generally occurs – weeks -> months
  – Occasionally may be limited
Prevention & treatment

• Avoidance of known risk factors / aggressive therapy of underlying condition
  – Sepsis management / source control
  – Hyperglycaemia
  – Drugs
  – Fever

• Avoidance of immobilisation
  – Reducing sedation, limiting paralysis
  – Early physiotherapy & mobilisation
  – Electrical muscle stimulation (EMS)

• Nutritional optimisation
Management (1) - hyperglycaemia

• Strict maintenance of blood sugar <6.1 mmol/L associated with improved mortality & reduced incidence of CIP [Van den Berghe G et al., NEJM 2001]

<table>
<thead>
<tr>
<th></th>
<th>CONVENTIONAL TREATMENT (N=783)</th>
<th>INTENSIVE TREATMENT (N=765)</th>
<th>P VALUE†</th>
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<tbody>
<tr>
<td>Electromyographic evidence of critical-illness polyneuropathy — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>At any time</td>
<td>107/206 (51.9)</td>
<td>45/157 (28.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>On more than 2 occasions</td>
<td>39/206 (18.9)</td>
<td>11/157 (7.0)</td>
<td>0.001</td>
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Positive linear correlation between risk of polyneuropathy and mean blood sugar level
Management (2) – drugs

• Steroids
  – use lowest dose effective & commence weaning rapidly (at 48 hrs)

• NMBAs
  – are probably NOT IMPLICATED as causal in neuromyopathies, however:
    – use intermittent doses rather than infusions
    – use agents not renal / hepatic excreted
    – monitor block

• β-stimulants
  – may cause myonecrosis
Management (3) – Fever & biochemical

• Fever
  – treat aggressively (over 40°C)

• Avoid:
  – hyperglycaemia
  – hypermagnesaemia
  – hyperosmolar states
  – hypokalaemia & hypophosphataemia
Prevention & treatment

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  – Hyperglycaemia
  – Drugs
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• Avoidance of immobilisation
  – Reducing sedation, limiting paralysis
  – Early physiotherapy & mobilisation
  – ?Electrical muscle stimulation (EMS)
Exercise in the ICU

[Needham DM et al., Crit Care Med 2009]
Electrical muscle stimulation prevents critical illness polyneuromyopathy: a randomized parallel intervention trial

Christina Routsi, Vasiliki Gerovasili, Ioannis Vasileiadis, Eleftherios Karatzanos, Theodore Pitsolis, Ell Tripodaki, Vasiliki Markaki, Dimitrios Zervakis and Seralim Nanas*

Abstract

Introduction: Critical illness polyneuromyopathy (CIPNM) is a common complication of critical illness presenting with muscle weakness and is associated with increased duration of mechanical ventilation and weaning period. No preventive tool and no specific treatment have been proposed so far for CIPNM. Electrical muscle stimulation (EMS) has been shown to be beneficial in patients with severe chronic heart failure and chronic obstructive pulmonary disease. Aim of our study was to assess the efficacy of EMS in preventing CIPNM in critically ill patients.

Methods: One hundred and forty consecutive critically ill patients with an APACHE II score ≥ 13 were randomly assigned after stratification to the EMS group (n = 68; age: 61 ± 19 years; APACHE II: 18 ± 4, SOFA: 6 ± 3) or to the control group (n = 72; age: 58 ± 18 years; APACHE II: 18 ± 5, SOFA: 9 ± 3). Patients of the EMS group received daily EMS sessions. CIPNM was diagnosed clinically with the medical research council (MRC) scale for muscle strength (maximum score 60, <48/60 cut-off for diagnosis) by two unblinded independent investigators. Duration of weaning from mechanical ventilation and intensive care unit (ICU) stay were recorded.

Results: Fifty-two patients could be finally evaluated with MRC: 24 in the EMS group and 28 in the control group. CIPNM was diagnosed in 3 patients in the EMS group as compared to 11 patients in the control group (OR = 0.22, CI: 0.05 to 0.92, P = 0.04). The MRC score was significantly higher in patients of the EMS group as compared to the control group (58 ± 15 vs. 52 ± 11; P = 0.04). The weaning period was statistically significantly shorter in patients of the EMS group vs. the control group (1 to 10 days vs. 3 to 41 days, respectively; median (range), P = 0.005).

Conclusions: This study suggests that daily EMS sessions prevent the development of CIPNM in critically ill patients and also result in shorter duration of weaning. Further studies should evaluate which patients benefit more from EMS and explore the EMS characteristics most appropriate for preventing CIPNM.

Trial Registration Number: Clinicaltrials.gov NCT00882830
Prevention & treatment

• Avoidance of known risk factors / aggressive therapy of underlying condition
  – Sepsis management / source control
  – Hyperglycaemia
  – Drugs
  – Fever

• Avoidance of immobilisation
  – Reducing sedation, limiting paralysis
  – Early physiotherapy & mobilisation
  – ?Electrical muscle stimulation (EMS)

• Nutritional optimisation
Early Parenteral Nutrition in Critically Ill Patients With Short-term Relative Contraindications to Early Enteral Nutrition: A Randomized Controlled Trial

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Importance Systematic reviews suggest adult patients in intensive care units (ICUs) with relative contraindications to early enteral nutrition (EN) may benefit from parenteral nutrition (PN) provided within 24 hours of ICU admission.

Objective To determine whether providing early PN to critically ill adults with relative contraindications to early EN alters outcomes.

Design, Setting, and Participants Multicenter, randomized, single-blind clinical trial conducted between October 2006 and June 2011 in ICUs of 31 community and tertiary hospitals in Australia and New Zealand. Participants were critically ill adults with relative contraindications to early EN who were expected to remain in the ICU longer than 2 days.

Interventions Random allocation to pragmatic standard care or early PN.

Main Outcomes and Measures Day-60 mortality; quality of life, infections, and body composition.

Results A total of 1372 patients were randomized (686 to standard care, 686 to early PN). Of 682 patients receiving standard care, 199 patients (29.2%) initially commenced EN. 186 patients (37.2%) initially commenced PN, and 278 patients (40.8%) remained...
Early PN: Results

- Standard care patients experienced greater muscle wasting (0.43±1.20 vs 0.27±1.17 SGA grade increase / week, \( p=0.01 \)) & greater fat loss (0.44±1.24 vs 0.31±1.21 SGA grade increase / week, \( p=0.04 \))

- Changes in MAMC were evident by day 2 (0.21±1.38 vs 0.00±1.31cm loss, \( p=0.04 \)), however these changes did not persist over the entire ICU stay
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21 – 23 April, Suntec Singapore

Intensive Care Pearls from East and West

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