ISSN: 2059-3341
EMRAN: Neuromuscular electrical stimulation review protocol
www.nottingham.ac.uk/emran

East Midlands Research into Ageing Network (EMRAN) Discussion Paper Series

ISSN 2059-3341

Issue 43, September 2021

Effects of neuromuscular electrical stimulation (NMES) in acutely hospitalised adult patients - protocol for a systematic review of randomised controlled trials (RCTs)

Alqurashi HB[1,2,3], Robinson K[1,3,4], Gladman JRF[1,3,4,5], Gordon AL[1,3,5,6], Masud T[3,4], Piasecki M[1,3]

East Midlands Research into Ageing Network (EMRAN) is a research collaboration across the East Midlands to facilitate applied research into ageing and the care of older people. EMRAN was set up with support from National Institute of Health Research Applied Research Collaboration East Midlands (NIHR ARC-EM)

Address for correspondence: Helal B Alqurashi, Division of Rehabilitation, Ageing and Wellbeing, B Floor Medical School, Queen's Medical Centre, Nottingham, NG7 2UH, UK. Email: Helal.Alqurashi@nottingham.ac.uk

Affiliations

[1] University of Nottingham, UK

[2] Taif University, Saudi Arabia

[3] NIHR Nottingham BRC, UK

[4] Nottingham University Hospitals NHS Trust, UK

[5] NIHR Applied Research Collaboration East Midlands, UK

[6] University Hospitals of Derby and Burton NHS Foundation Trust, UK

ORCID

Alqurashi HB: 0000-0002-4281-7700

Robinson, K: 0000-0003-1458-8186

Gladman, JRF: 0000-0002-8506-7786

Gordon, AL: 0000-0003-1676-9853

Masud, T: 0000-0003-1061-2898

Piasecki, M: 0000-0002-7804-4631

ISSN: 2059-3341
EMRAN: Neuromuscular electrical stimulation review protocol
www.nottingham.ac.uk/emran

ABSTRACT

Introduction

Hospitalised patients are at high risk of loss of muscle mass and function as a consequence of a period of immobilisation, due to fractures or other conditions requiring surgery or critical care. These adverse outcomes can be attenuated by resistance exercise but performing and adhering to the required exercise programme can be challenging and difficult for this population. The technique of neuromuscular electrical stimulation (NMES) may be employed as an alternative to exercise in preventing or reversing the loss of muscle mass and/or function.

Objective

To examine the evidence for the effects of NMES applied to one or more limbs in acutely hospitalised adult patients.

Method

MEDLINE, EMBASE, Cumulative Index to Nursing & Allied Health (CINAHL) and the Cochrane library will be searched for relevant studies. Inclusion criteria: randomized controlled trials (RCTs) of hospitalised adult patients (aged ≥ 18 years) comparing NMES alone or with other interventions to usual care or other interventions. Our primary outcome of interest is muscle strength, and our secondary outcomes include but not limited to the following outcomes and categories: muscle mass, molecular and cellular function, hospital length of stay and adverse effects. Two reviewers will independently screen the titles and abstracts, then full texts against the eligibility criteria. Data extraction, critical appraisal and synthesis will be conducted using Review Manager (RevMan) software. Quality of evidence and rating will be assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. Meta-analysis will be conducted where possible, otherwise a synthesis without meta-analysis will be conducted, based upon the volume of evidence, its quality and effect sizes observed.

INTRODUCTION

The loss of muscle mass and function associated with ageing is known as sarcopenia. Rapid loss of mass and function can be observed in adults hospitalised with acute conditions such as fractures, acute respiratory diseases, heart failure, kidney dysfunction or any condition requiring surgery or critical care – this is often referred to as secondary sarcopenia [1] and may be due to immobilisation, inflammation and dietary inadequacies [2]. Secondary sarcopenia can lead to the limitations in activities, called hospital-associated disability [3], and this can lead to an extended length of hospital stay, health risks due to disability itself and, potentially, long term disability. Early physical activity and mobilisation play an essential role in acute care, aiming to prevent this cascade of consequences [4].

The effects of exercise on muscle mass and function in hospitalised patients have been extensively investigated. Improvement in activities of daily living, walking, health-related quality of life, and muscle strength have been observed in patients hospitalised for chronic obstructive respiratory disease after a period of combined exercise/rehabilitation (stretching, resistance, and aerobic exercises) [5] and resistance exercise alone [6]. Additionally, increase in muscle mass after whole body heavy resistance exercise has been detected in hospitalized patients on geriatric medicine wards [7]. Despite the promising effects of exercise, the implementation of such protocols can be challenging because patients who are hospitalised may be medically unstable or receiving therapy [8]. Furthermore, the reasons for admission to hospital can include pain, immobilisation, fatigue and cardio-respiratory symptoms, which can both be barriers to exercise and counted as adverse events in hospitalised patients who have been prescribed exercise interventions [9]. Therefore, alternative techniques should be explored, instead of or in addition to exercise, to mitigate against loss of muscle mass and function acquired after hospitalisation.

Neuromuscular Electrical Stimulation (NMES) is a technology that enables involuntary muscle contraction using non-invasive, low-frequency current, and can be performed with or without voluntary effort [10]. NMES parameters includes frequency (Hz), pulse duration (microseconds, μs), pulse amplitude (millivolts or milliamperes), work-rest cycle (ON:OFF ratio), session duration (min), session frequency (days/week) [10]. Pilot searches conducted by Alqurashi in 2021 searching Medline for systematic reviews and NMES

identified 88 separate review articles, concerning many different biological, muscular and functional outcomes, in different populations (children, adults, athletes, old adults) and in both healthy volunteers and patients with a variety of conditions. These reviews examined the effect of NMES on patients with neurological disorders (stroke, spinal cord injury) [11, 12], knee osteoarthritis and arthroplasty [13, 14], chronic obstructive respiratory disease [15], heart failure [16], cancer [17], kidney failure [18], swallowing [19], speech [20] and oedema [21]. There were two reviews focussed upon critically ill hospitalised patients [22, 23]. Another review focused on interventions for secondary sarcopenia in older people in hospital [24], which included three studies on the use of NMES. No review was found specifically focussed upon the effects of NMES to maintain or restore limb function in adults admitted to hospital with acute conditions. However, a protocol for such a review on the PROSPERO database of systematic reviews [25] was identified. This systematic review, like the one listed on the PROSPERO database, aims to examine the evidence of the effects of NMES applied to one or more limbs in acutely hospitalised adult patients. In comparison with the registered review, this review will include NMES together with other interventions and for the comparator arm, this review will include other non-placebo comparator groups (e.g. usual care including exercise or nutrition). Further, this review will include a broad range of outcomes and a broader range of study publication dates.

METHOD

This protocol was written in accordance with the PRISMA-P reporting guideline [26], and it has been registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42021259763).

Eligibility criteria

Inclusion criteria

- Participants: adults and older adults (aged ≥ 18 years) who are admitted to hospital with acute medical or surgical conditions.
- Intervention: NMES applied to a limb alone or combined with different interventions.
- Control: no treatment, sham, or other usual treatments.
- Outcomes: including one or more of the outcomes of interest.
    - Primary outcomes
        - Muscle strength

- Secondary outcomes, including but not limited to the following outcomes and categories
  - Muscle mass
  - Molecular and cellular (e.g. muscle fibre type composition, insulin-like growth factor 1 (IGF-1), immunohistochemical fibre denervation markers or satellite cells)
  - Function (e.g. gait speed or disability)
  - Hospital length of stay
  - Adverse effects (e.g. discomfort or pain)
- Design: randomized controlled trials (RCTs) and quasi-randomized controlled trials.

Exclusion criteria

- Participants: patients selected due to psychiatric conditions, speech, swallowing or facial disorders.
- Intervention: NMES not applied to a limb (e.g. solely applied to treat facial, swallow or speech problems). We will not include studies using electrical stimulation used for its afferent effect (such as for pain or spasticity) rather than to produce muscular stimulation, which will classify as transcutaneous elections stimulation (TENS). We will not include studies using pulsed electrical stimulation to augment normal movement such a functional electrical stimulation (FES).
- Control: no control group, or comparisons only between different NMES parameters.
- Reporting: not published in English.

Information sources

We will search the following electronic databases: MEDLINE, EMBASE, Cumulative Index to Nursing & Allied Health (CINAHL) and the Cochrane library.

Search strategy

The key words that will use to perform the search are: adults AND hospitalised AND critically ill AND neuromuscular electrical stimulation. The reference lists of the selected studies will be searched for additional studies.

Study records: data management

Endnote 9 will be used to import research results and remove duplications. Results will then be transferred to Rayyan intelligent systematic review software for screening titles and abstracts, recording the reasons for exclusion, storing the full texts.

Selection process

Two reviewers will independently screen the titles and abstracts against the eligibility criteria. From those included at this stage, two reviewers will independently screen the full-text articles against the eligibility criteria. Any disagreements will be resolved by discussion or by a third reviewer.

Data extraction

Two reviewers will independently perform data extraction for all included studies by using a standardised data extraction table. The information extracted will include study information (first author, year of publication, country, design), participant characteristics (total sample size, gender, age, body mass index), intervention group (sample size, gender, age, detailed protocol parameters, additional intervention), control group (sample size, gender, age, intervention type), outcome measures, results.

Risk of bias assessment

Two reviewers independently will perform risk of bias assessments. The risk of bias for each study will be assessed using the Cochrane Collaboration risk of bias assessment tool for randomised trials [27] which takes account of: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Each aspect will be graded as three levels; low, unclear, and high risk of bias.

Quality assessment

We will analyse the quality of the evidence available for each outcome of interest using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [28]. This will assess: study limitations/risk of bias, inconsistency of results, indirectness of evidence, imprecision and reporting bias. Then the quality of the evidence for each outcome will be classified as high, moderate, low or very low.

Data analysis and synthesis

The nature and extent of the research evidence will be summarised using a standardised table, including: number of studies and patients, date, place, size, population, intervention, and outcome. If three or more studies with similar intervention investigate the same outcome domain using comparable measures, meta-analysis will be conducted. Review Manager (RevMan) software will be used. Mean difference or standardised mean difference, 95% confidence intervals and two-sided P values will be calculated to measure the treatment effect for each outcome. We will assess heterogeneity using the I^2 statistic as the following: if the value of I^2 less than 50% indicating acceptable heterogeneity, we will utilize a fixed-effect model. I^2 greater than 50% means significant heterogeneity and we will use a random-effect model.

If the criteria for meta-analysis are not met, a synthesis without meta-analysis (SWiM) will be conducted. The SWiM will take account of two elements: the quality of the evidence and the effect size. Each of the selective studies will be given a quality rating of low quality, moderate quality, and high quality depending on assessment of study quality.

Good quality: low risk of bias and sample size > 40

Moderate quality: high risk of bias and sample size > 40

Low quality: high risk of bias and sample size < 40

The effect sizes (*d*) of each study and outcome will be calculated by the following equation (divide the difference between intervention group mean and control group mean by standard deviation), and then classified using Cohen's classification whereby $d < 0.2$ "no effect", $d = 0.2\text{-}0.49$ "small effect", $d = 0.5\text{-}0.79$ "moderate effect", and $d \geq 0.8$ *"large effect" [29].*

According to quality and effect size, we will interpret the result for each outcome to answer our research question by using the following classification

- No evidence (no studies have examined this outcome)
- Evidence of no effect (no effect showed by one or more studies of moderate or good quality)
- Evidence of small effect (small effect showed by one or more studies of moderate or good quality)
- Evidence of moderate effect (moderate effect showed by one or more studies of moderate or good quality)

- Evidence of large effect (large effect showed by one or more studies of moderate or good quality)
- Inconsistent evidence (differing results and effect sizes between two or more studies of moderate or good quality)

DISCUSSION

Loss of muscle and disability is very common among hospitalised patients [1-3]. Previous studies suggested that NMES can preserve muscle mass and function. However, no systematic reviews investigated the effectiveness and safety of NMES in hospitalised patients. Therefore, this planned review will systematically explore the evidence of the effects of NMES in adults acutely admitted to hospital. The results of this study will supply high-quality evidence and recommendations for clinicians and scientific researchers.

A potential limitation of this systematic review is that it will include only published trials and exclude unpublished data. However, although it has been suggested to include unpublished studies, the inclusion of these studies can introduce bias by itself. Further, unpublished studies are usually smaller and have poorer methodological quality than peer-reviewed trials [30]. Another limitation is the reliance on English-language studies only. However, Morrison et al. [31] conclude that although English-language restriction may reduce the total amount of literature found, it does not introduce bias. We have anticipated the potential limitation that a numerical synthesis (meta-analysis) may not be possible for many or all the outcomes of interest due to different ways of measuring outcomes. Therefore, we have planneda synthesis without meta-analysis based upon the amount, quality and effect sizes found.

ACKNOWLEDGEMENTS

This study was supported by the NIHR Nottingham Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.
HA was supported by grant from Taif University, Saudi Arabia.
The authors have no conflicts of interests to declare.

REFERENCES

1. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.
2. Zinglersen AH, Halsteen MB, Kjaer M, Karlsen A. Can electrical stimulation enhance effects of a functional training program in hospitalized geriatric patients? Exp Gerontol. 2018;106:101-8.
3. Martinez-Velilla N, Saez de Asteasu ML, Ramirez-Velez R, Zambom-Ferraresi F, Garcia-Hermoso A, Izquierdo M. Recovery of the decline in activities of daily living after hospitalization through an individualized exercise programme: secondary Analysis of a Randomized Clinical Trial. Journals of gerontology Series A, Biological sciences and medical sciences. 2021.
4. Miranda Rocha AR, Martinez BP, Maldaner da Silva VZ, Forgiarini Junior LA. Early mobilization: Why, what for and how? Med Intensiva. 2017;41(7):429-36.
5. José A, Dal Corso S. Inpatient rehabilitation improves functional capacity, peripheral muscle strength and quality of life in patients with community-acquired pneumonia: a randomised trial. J Physiother. 2016;62(2):96-102.
6. Borges RC, Carvalho CR. Impact of resistance training in chronic obstructive pulmonary disease patients during periods of acute exacerbation. Arch Phys Med Rehabil. 2014;95(9):1638-45.
7. Norheim KL, Cullum CK, Andersen JL, Kjaer M, Karlsen A. Inflammation Relates to Resistance Training-induced Hypertrophy in Elderly Patients. Med Sci Sports Exerc. 2017;49(6):1079-85.
8. Camp PG, Reid WD, Chung F, Kirkham A, Brooks D, Goodridge D, et al. Clinical Decision-Making Tool for Safe and Effective Prescription of Exercise in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: Results From an Interdisciplinary Delphi Survey and Focus Groups. Phys Ther. 2015;95(10):1387-96.
9. Rice H, Harrold M, Fowler R, Watson C, Waterer G, Hill K. Exercise training for adults hospitalized with an acute respiratory condition: a systematic scoping review. Clin Rehabil. 2020;34(1):45-55.
10. Nussbaum EL, Houghton P, Anthony J, Rennie S, Shay BL, Hoens AM. Neuromuscular Electrical Stimulation for Treatment of Muscle Impairment: Critical Review and Recommendations for Clinical Practice. Physiother Can. 2017;69(5):1-76.
11. Lee JH, Baker LL, Johnson RE, Tilson JK. Effectiveness of neuromuscular electrical stimulation for management of shoulder subluxation post-stroke: a systematic review with meta-analysis. Clin Rehabil. 2017;31(11):1431-44.
12. Bekhet AH, Bochkezanian V, Saab IM, Gorgey AS. The Effects of Electrical Stimulation Parameters in Managing Spasticity After Spinal Cord Injury: A Systematic Review. Am J Phys Med Rehabil. 2019;98(6):484-99.
13. de Oliveira Melo M, Aragão FA, Vaz MA. Neuromuscular electrical stimulation for muscle strengthening in elderly with knee osteoarthritis - a systematic review. Complement Ther Clin Pract. 2013;19(1):27-31.
14. Yue C, Zhang X, Zhu Y, Jia Y, Wang H, Liu Y. Systematic Review of Three Electrical Stimulation Techniques for Rehabilitation After Total Knee Arthroplasty. J Arthroplasty. 2018;33(7):2330-7.
15. Wu X, Hu X, Hu W, Xiang G, Li S. Effects of neuromuscular electrical stimulation on exercise capacity and quality of life in COPD patients: a systematic review and meta-analysis. Biosci Rep. 2020;40(5).
16. Gomes Neto M, Oliveira FA, Reis HF, de Sousa Rodrigues E, Jr., Bittencourt HS, Oliveira Carvalho V. Effects of Neuromuscular Electrical Stimulation on Physiologic and

Functional Measurements in Patients With Heart Failure: A SYSTEMATIC REVIEW WITH META-ANALYSIS. J Cardiopulm Rehabil Prev. 2016;36(3):157-66.
17. O'Connor D, Caulfield B, Lennon O. The efficacy and prescription of neuromuscular electrical stimulation (NMES) in adult cancer survivors: a systematic review and meta-analysis. Support Care Cancer. 2018;26(12):3985-4000.
18. Schardong J, Stein C, Della Méa Plentz R. Neuromuscular Electrical Stimulation in Chronic Kidney Failure: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil. 2020;101(4):700-11.
19. Alamer A, Melese H, Nigussie F. Effectiveness of Neuromuscular Electrical Stimulation on Post-Stroke Dysphagia: A Systematic Review of Randomized Controlled Trials. Clin Interv Aging. 2020;15:1521-31.
20. Almeida ANS, Cunha DAD, Ferreira SLS, Guimaraes BTL, Balata PMM, Silva HJD. Effect of Electrical Stimulation on the Treatment of Dysphonia: A Systematic Review. J Voice. 2020;28:28.
21. Burgess LC, Immins T, Swain I, Wainwright TW. Effectiveness of neuromuscular electrical stimulation for reducing oedema: A systematic review. J Rehabil Med. 2019;51(4):237-43.
22. Zayed Y, Kheiri B, Barbarawi M, Chahine A, Rashdan L, Chintalapati S, et al. Effects of neuromuscular electrical stimulation in critically ill patients: A systematic review and meta-analysis of randomised controlled trials. Aust Crit Care. 2020;33(2):203-10.
23. Trethewey SP, Brown N, Gao F, Turner AM. Interventions for the management and prevention of sarcopenia in the critically ill: A systematic review. J Crit Care. 2019;50:287-95.
24. Welch C, Majid Z, Greig C, Gladman J, Masud T, Jackson T. Interventions to ameliorate reductions in muscle quantity and function in hospitalised older adults: a systematic review towards acute sarcopenia treatment. Age Ageing. 2021;50(2):394-404.
25. Mariana Lanzoni Campos, Tayla Siqueira Ruy, Leilane Marcos. Effects of neuromuscular electrical stimulation in hospitalized patients: A systematic review. PROSPERO 2020 CRD42020200993 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020200993
26. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. Bmj. 2021;372:n160.
27. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.
28. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.
29. Coe R, editor It's the effect size, stupid. Paper presented at the British Educational Research Association annual conference; 2002.
30. Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technol Assess. 2003;7(1):1-76.
31. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28(2):138-44.