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Feasibility RCT of neuromuscular electrical stimulation; an Intervention to Maintain and improve neuroMuscular function during periods of Immobility (IMMI): Protocol.

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ABSTRACT

Introduction

Functional recovery from fragility fractures such as those of the lower limb, hip or spine in older people with frailty is often limited. Patients often have pre-fracture muscle weakness, which worsens due to the injury, and both pain and general ill health interfere with resistance exercise which is the mainstay of motor recovery. One possible adjunct to rehabilitation in such people is neuromuscular electrical stimulation (NMES), which can stimulate muscles while the patient is resting. The feasibility of NMES in older people with fragility fractures has not previously been determined, nor is it yet clear whether such patients require additional protein supplementation to benefit from NMES. We present a protocol for such a feasibility study that will also examine the need for additional protein supplementation.

Method

Participants will be patients in hospital with reduced mobility due to fragility fractures of the spine, pelvis, hip or lower limb. A randomised controlled feasibility trial will be conducted in which participants will be randomised either to have the left or right leg stimulated using NMES and therefore using the non-stimulated leg as a control, and also randomised either to have or not have an oral protein supplement during treatment sessions. NMES sessions will be daily until discharge from hospital to a maximum of 6 weeks. Outcomes will include measures of efficacy of NMES at the muscular impairment level (strength, muscle ultrasound parameters, intramuscular electromyographic parameters), feasibility outcomes (recruitment and retention rates, compliance and tolerability), and measures of potential outcomes for future trials (pain, mobility, disability).

Discussion

This study is a necessary step before NMES can be included in a multimodal intervention package to optimise recovery after fragility fracture.

Key words

Sarcopenia, Frailty, Immobility, Electrical Stimulation, Protein supplementation

INTRODUCTION

Sarcopenia

Extensions in human longevity in western countries since industrial times have not only led to longer periods of life spent in good health, but have also been associated with increasing periods of time spent in poor health at the end of life. The average UK man and woman, with life expectancies of 79 and 83 respectively, spend around 13 and 19 years respectively at the end of life in poor health [1]. It would be desirable to minimise the amount of time spent in poor health - for the health span to be closer to the lifespan.

Muscular weakness leading to loss of function is a major contributor to poor health in these years towards the end of life [2]. The loss of muscle strength, quality and mass seen with advancing age is "sarcopenia". Sarcopenia is one of the most important deficits associated with frailty – the vulnerability state seen with ageing that leads to, and is associated with, disability and other health problems. Sarcopenia, like other age-associated changes, is a consequence of genetic factors interplaying with numerous known and unknown environmental and behavioural factors. Regular exercise is protective against the development of sarcopenia. Being sedentary also, and additionally, contributes to sarcopenia. Intervention studies show that resistance exercise training at least partly reverses sarcopenia, even in extreme old age.

The muscle protein synthetic response to resistance exercise is reliant upon adequate amount of habitual dietary protein intake. The average western adult diet has approximately twice the amount of protein specified in dietary guidelines [3], and protein deficiency in clinical practice is generally associated with severe protein malabsorption or protein losing conditions. Guidelines for protein requirements for older people are generally higher than for younger adults (in terms of grams of protein per kilogram body weight). This is because of "anabolic blunting", the age-associated reduction in the ability to synthesise muscle protein in response to a given protein load and exercise challenge [4]. However, guidelines do not currently advise specific protein supplementation as a treatment to prevent or reverse sarcopenia.

Sarcopenia in hospitalised patients

Many older people, especially those with frailty and hence existing sarcopenia, are admitted to hospital with conditions that render them immobile. Examples include a

fracture of the hip, spine, pelvis, or leg after a fall, but almost any medical illness in an older person with frailty can lead to a loss of function such that they become immobile. The period of immobility after such conditions depends upon the prior function and strength of the individual, the amount of pain, general health issues and access to rehabilitation, and can vary from a day, to several weeks. Occasionally the loss of mobility can be permanent. Periods of immobility, whatever the cause, lead to further loss of muscle mass and strength – disuse atrophy [5]. This process may be even more rapid in hospitalised patients due to the effects of inflammation and illness, which may depress muscle metabolism further. Furthermore, if immobility is for extended periods and energy intake remains unchanged then disuse atrophy leads to whole-body and muscle fat mass gain, both of which are associated with poor health outcomes. Patients will not return to prior levels of physical function and body composition unless they reverse these immobility-induced changes and, some will never become mobile again.

Usual clinical care on geriatric and orthopaedic wards is to mobilise such patients as soon as possible, to keep them mobilised, to avoid bed rest to reduce the amount of sedentary behaviour, and to optimise their diets. Patients who are not mobile are advised to do chair based or seated exercises. The limited evidence about the benefit of such exercises suggests that they are of little value [6]. Part of the reason for this is that they are difficult to perform in adequate intensity when patients are ill, tired, or in pain. These same factors may reduce appetite. However, in line with the current evidence-base and consensus opinions, clinical teams do not routinely offer nutritional supplements to all older immobile patients, but reserve them for those who do not consume a diet that meets recommended dietary guidelines.

Possible approaches to improving outcome

A review of approaches to loss of muscle function in hospitalised patients identified several potential therapeutic options beyond resistance exercise and optimal diet: drug therapy (e.g. anabolic steroids, growth hormone), neuromuscular electrical stimulation, and oral protein supplementation [7]. This review showed that there is promising evidence that each of these interventions could improve outcomes, but the evidence is insufficient for any of them to apply them routinely in clinical practice. However, there is sufficient evidence of benefit to advise that resistance exercise should be encouraged as much as possible.

This study

In this study, we aim to evaluate the effect of neuromuscular electrical stimulation as an addition to best care in people admitted to hospital who have reduced mobility due to a fragility fracture. Given concerns that the potential benefits of this treatment may be limited by dietary protein intake, we will study this with and without a high protein oral nutritional supplement. We have chosen not to study drug therapy as well: safety concerns will limit the applicability and desirability of this mode of treatment, whereas neuromuscular stimulation, with protein supplementation if required, is likely to be suitable for widespread use.

Neuromuscular electrical stimulation

The variant of neuromuscular electrical stimulation we will test involves a small electric current applied via a pad applied to the skin overlying the nerves supplying the muscles of the leg while the patient is lying in bed. A trained operator applies treatment to one leg, for approximately 30 minutes per session, three sessions per week. The electrical current goes through the pad and skin and stimulates the underlying nerves, which in turn stimulate the muscles supplied by those nerves to contract and thus then stimulates muscle growth and the associated metabolic responses that prevent loss of muscle. Treatment can stimulate the nerve controlling the vastus lateralis muscle in the thigh or the nerve controlling the tibialis anterior muscle in the lower leg, or both. In our study, we will aim to stimulate both nerves and muscle groups, on the basis that the maximal effect with result from the maximal amount of muscle stimulated. One of our feasibility questions will be to determine the degree to which we can achieve this aim. The stimulation may also stimulate the central nervous system (spine and brain via afferent pathways) and create adaptive change in these tissues as well, and these effects may reduce pain and hence have a bearing on the ease with which patients can perform exercise (pain will be a secondary outcome). However, the main mechanism responsible for beneficial effects on strength is at the level of the muscle. Stimulation via the nerve recruits a larger amount of muscle than other forms of stimulation such as those applied over the muscle itself: this is important because the greater the amount of muscle stimulated the more likely we will achieve a meaningful clinical effect. It is usual to start sessions with small electrical currents initially and to ramp this up gradually within a session - this develops tolerance to the initial uncomfortable sensations that some patients can experience. Treatment is adjusted to generate a specific force and maintained for up to 5 minutes, followed by a rest period and then repeated three times over the typical 30-minute session. The

stimulation can vary according to the frequency (pulses per second, typically 10-50Hz). Pulses vary in width and intensity and these parameters can affect both comfort and the amount of muscular activation achieved: wider pulse widths tend to be the most comfortable. Over-stimulation can lead to fatigue, a loss of force resulting from stimulation greater than that needed to achieve beneficial adaptation. We will adjust the level of stimulation to the level of muscle force generated by the target muscle. We will reassess this at regular intervals to account for adaptation to the stimulation. There is no recognised optimal specific set of these parameters that optimises contraction and comfort and avoids fatigue, which is why we will individualise these parameters in each individual. Neuromuscular electrical stimulation is widely advertised as a treatment modality used in physiotherapeutic practice in people of a wide range of ages and conditions, and in athletes [9]. This indicates that it is generally a safe technique although avoided in pregnancy for precautionary reasons, in those with implanted electrical devices to avoid interference, and where there are moist skin lesions or wounds where the skin pad is to be applied. The evidence for its effectiveness from controlled studies, particularly in older people with frailty, is limited. There have been promising studies conducted in oropharyngeal dysphagia and foot drop after stroke, in the sarcopenia (loss of muscle) associated with COPD and kidney failure, in osteoarthritis of the knee and after elective knee and hip surgery. The lack of large-scale studies with clinical outcomes means that widespread adoption of the technique and optimisation of the potential health gain from it is not yet justifiable [9].

We propose to use neuromuscular electrical stimulation during initial periods of immobility in older people after a fracture, and to continue it during the periods of bed rest until the patient is discharged, or for a maximum of 6 weeks (representing the main recovery period). Although neuromuscular electrical stimulation could play a valuable role in the development or maintenance of further rehabilitation gains, this would require a different, longer-term, study. This is why we are not extending the intervention phase beyond discharge in this study.

In this study, we will stimulate one of the participants' legs, using the other leg as a control comparison. Allocation of which leg is stimulated with be on a randomised basis to avoid allocation biases and will ensure that we will apply NMES to legs affected by injury as well as those without - as would be anticipated in usual, bilateral clinical practice. Whilst in a clinical efficacy study we would aim to stimulate both legs, in this study our outcomes include the feasibility and acceptability of NMES, which we believe we will answer

appropriately by single leg stimulation. Our primary efficacy measures in this study are at the single limb level – later trials (if justified) will have primary outcomes relevant to bilateral stimulation such as gait speed and disability.

Additional protein supplementation: high protein supplement

Neuromuscular electrical stimulation alone (in the presence of usual nutritional support) may be sufficient to improve outcome, and studies to date in community dwelling patients have not required additional protein supplementation. However, many older patients in hospital consume an inadequate diet. Our audits have shown that patients with hip fractures consume about 1/3 of their daily requirement of calories and less than ½ their daily requirement of protein [8]. Protein is required around the time of exercise so that amino-acids (the building blocks of proteins) are circulating in the blood stream ready to be incorporated into muscle protein during the hour or two after exercise. If there are inadequate levels of amino acids either because not enough protein is being consumed or if it is being used to provide energy (i.e. as calories) then neuromuscular electrical stimulation could fail to improve muscle function. We propose to overcome this potential problem by offering single doses of a high protein supplement after each bout of neuromuscular electrical stimulation. We appreciate that this does not solve the general problem of under-nutrition in hospital, and that much more research and development is required to solve that issue. However, by studying the effect of neuromuscular electrical stimulation with and without additional protein, we will establish whether future trials of neuromuscular electrical stimulation need to include protein supplementation as a necessary part of the overall treatment. We will randomly allocate participants offering half of them additional protein supplementation over and above their ordinary diet. In this way, we will be able to observe the effect at the muscle level of neuromuscular stimulation (a comparison between legs), and its effect with and without additional protein supplementation (on a randomised basis). Oral Nutritional Supplements (ONS), which are widely used within the acute and community health settings for individuals who are unable to meet their nutritional requirements through oral diet alone. A single (100g) portion of high protein supplement gives approximately 20g protein.

Purpose, aim and objectives

The overall purpose of this research is to contribute to minimising the impact of frailty by reducing muscle weakness. The aim of this study is to determine whether it is justifiable to conduct a large-scale clinical trial of neuromuscular electrical stimulation with or without

additional protein supplementation in hospitalised patients who are temporarily immobilised following a fragility fracture. The objectives of the study are

1. to determine the proportion of patients with fragility fractures who will consent to this study, and their characteristics

2. to determine the compliance with and acceptability of neuromuscular electrical stimulation treatment and participant characteristics affecting this

3. to determine the compliance with and acceptability of protein supplementation and participant characteristics affecting this

4. to determine the short term effect of neuromuscular electrical stimulation with or without additional protein supplementation upon measures of neuromuscular function and structure, and the effect of compliance with treatment upon these measures

5. to determine recruitment parameters and suitable outcome measures for a subsequent RCT with clinical outcomes

METHOD

Study setting

The study will be performed at hospital trauma and geriatric medical wards in Nottingham University Hospitals NHS Trust.

Study Participants

Inclusion criteria:

- >/=65 years
- Hospitalised due to incident fragility fracture (hip, spine, pelvis, rib, upper limb, lower limb)
- New mobility status as a consequence of the fracture
- Not expected to be discharge within 7 days of recruitment

Exclusion criteria:

Subjects will be excluded from this proposed study if they are:

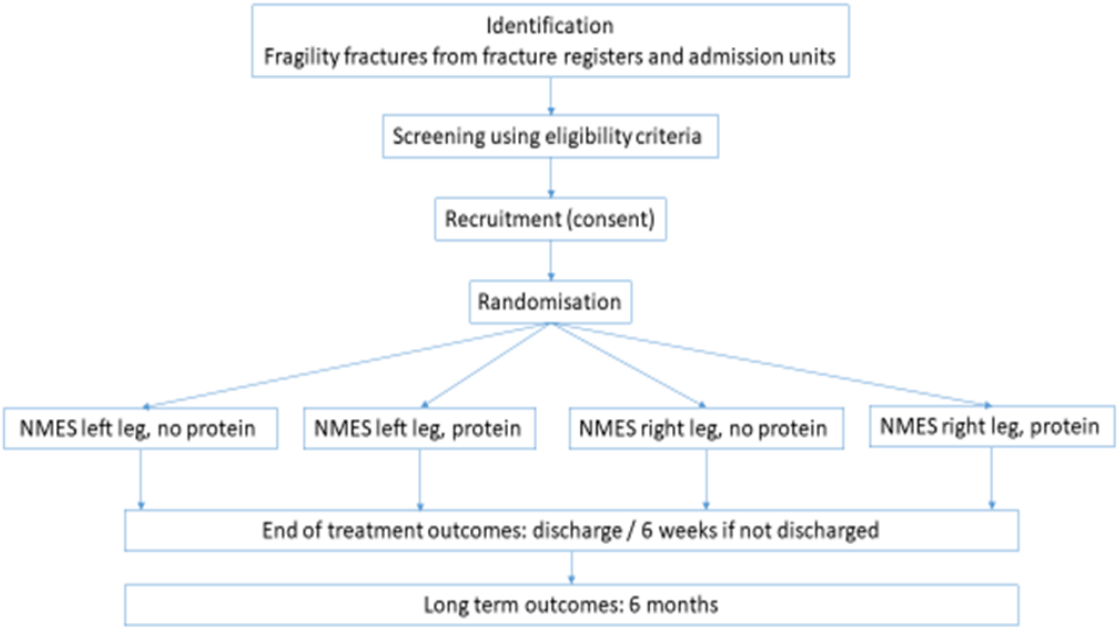
- Unable to give valid informed consent (later work may explore the option of treating such people)

- Resident outside catchment area of hospital (likely to be moved during the study period)
- Unable to communicate in English sufficiently to participate in neuromuscular electrical stimulation
- Implanted medical device (e.g. pacemaker)
- Any other contraindications to neuromuscular electrical stimulation (e.g. injury to all stimulation sites)
- Leg amputation or any pre-injury conditions affecting a leg unilaterally such as hemiparesis
- Dysphagia for liquids
- End stage renal failure (dialysis)
- Obesity (BMI>30)
- End of life, for any reason
- Any other clinical reason why rehabilitation is not clinically indicated

Study design

This study is Feasibility RCT. A parallel group RCT design and will be conducted over a period of 15 months. We will offer all recruited participants neuromuscular electrical stimulation (NMES) to one leg (see Figure 1).

Figure 1. Study design flow chart



Sample size:

Our proposed total sample size is 60 participants. Sample size calculations are typically not required for many feasibility study outcomes where statistical testing is not required. Sample sizes of 20 are usually sufficient to estimate recruitment rates and examine the suitability of outcome measures.

Participant identification and screening

Potential participants will be identified from hospital fracture registers and from hospital trauma and geriatric medical wards by Clinical Research Network (CRN) staff. The CRN staff will apply the eligibility criteria as far as possible by consulting their medical records, their attending health care professionals. They will keep an anonymised screening log of potential participants, recording the date of screening, place of screening and hospital number of all participants with eligible fractures (to avoid repeated screening of potential participants) and the exclusion criteria applied.

Randomisation

Research staff will approach potential participants identified as above, and re-apply the eligibility criteria. Written consent will be required. After the collection of baseline data, consenting participants will be randomly allocated, using the online "Sealed Envelope" randomisation service, to one of four equal groups (NMES = neuromuscular electrical stimulation):

- NMES left leg, no high protein supplementation
- NMES left leg, high protein supplementation
- NMES right leg, no high protein supplementation
- NMES right leg, high protein supplementation

Measurements

There is no single, primary endpoint, but several outcomes of interest:

- Recruitment rate: We will calculate this by comparing the number of recruits to those identified by the screening logs and examine their characteristics by examining the exclusion criteria.
- Number of treatment sessions, duration of treatment sessions, period over which treatment sessions are delivered, maximal intensity of stimulation during treatment sessions, proportion of participants stimulated in thigh / lower leg / both, reasons for missing sessions: This will serve to determine the compliance with and acceptability of neuromuscular electrical stimulation treatment and participant characteristics affecting this.
- Number of protein supplementation doses consumed and acceptability questionnaire of NMES**:** This is to determine the compliance with and acceptability of NMES and participants' characteristics affecting this. At the end of each session, the patients will be asked to complete a short verbal questionnaire. They will be asked: If they would consider NMES as an acceptable treatment for lower limb weakness after a period of immobilisation.
- Tolerability questionnaire: At the end of each session, the patients will be asked to complete a short verbal questionnaire. They will be asked: to give a verbal categorical rating of the NMES treatment, as: 'very comfortable', 'comfortable', 'bearable' or 'unbearable'**.** If they noticed a difference in the sensation due to stimulation between the operated limb and the contralateral limb.

- Ultrasound parameters: Using a portable bedside device to determine the short-term effect of neuromuscular electrical stimulation (thickness, pennation angle, echogenicity). Ultrasound is well tolerated. Conducting gel is applied to the skin and the scanner is pressed against the muscle and moved until good images are obtained. The whole process will take 20 minutes.
- Intramuscular electromyography(iEMG): Intramuscular electromyography (iEMG) is another measure of the potential effect of neuromuscular electrical stimulation. We will perform intramuscular electromyography (iEMG), in both legs, at the first treatment session and the last treatment session to determine the change in these variables. The whole process will take 20 minutes.
- A hand-held dynamometer: is a portable measurement device to assess Lower limb muscle strength.
- Elderly Mobility Scale: This is a simple 20-point measure of mobility which is widely used to assess the overall mobility in frail older people [9].We will apply the Elderly Mobility Scale in the last treatment session before discharge.
- Hand grip strength: using Jamar Hydraulic Hand Dynamometer to measure isometric force and peak strength with five adjustable grip positions. It has a consistently strong relationship to function, sarcopenia and frailty [10].
- Visual analogue scores for pain**:** We will use the Numerical Rating Scale (NRS) [11] on the first and last treatment session. This is a 0-10 scale where respondents are asked to rate, for each leg, the current level of pain and the least, worst and average level of pain over the previous 24 hours.

Outcome measures at 6 months after recruitment:

- Barthel ADL score: Designed to assess participants' dependency, it is a 10 item questionnaire of personal ADL [12]. Research staff will collect the personal ADL by telephone or by post if necessary.
- Nottingham Extended ADL: designed to assess participants dependency, is a 22 item questionnaire of functional mobility, household and social activity [13]. Research staff will collect the instrumental ADL by telephone or by post if necessary.
- Length of hospital stay: from hospital records.
- Readmission rate: from hospital records.
- Discharge destinations: from hospital records.
- Mortality: from GP and hospital records.

Interventions

These interventions will be provided additional to participants' optimised care. A separate protocol for each intervention will be provided at the appendices section:

Neuromuscular electrical stimulation

Before the NMES application, warming exercises will be performed on the lower extremity muscles for 5 minutes. The variant of neuromuscular electrical stimulation we will test involves a small electric current applied via a skin electrode overlying the nerves supplying the muscles of the leg while the patient is lying in bed, positioned in supine with the knee in full extension. Quadriceps will be stimulated on the sound leg for 30 min, 3 days per week for 6 weeks or until discharged from hospital. Treatment is adjusted to generate a specific force and maintained for up to 5 minutes, followed by a rest period and then repeated three times over the typical 30-minute session. The stimulation can vary according to the frequency (pulses per second, typically 10-50Hz). In this study, we will stimulate one of the participants' legs, using the other leg as a control comparison.

Additional protein supplementation: high protein supplementation (ONS).

We will randomly allocate participants offering half of them additional protein supplementation over and above their ordinary diet. In this way, we will be able to observe the effect at the muscle level of neuromuscular stimulation (a comparison between legs), and its effect with and without additional protein supplementation (on a randomised basis). Evidence from many sources indicated that 20g protein after a bout of exercise is the maximum amount that can possible be metabolized [10]. A standard (100g) portion of ONS gives 20g protein.

Data analysis

Between group statistical testing will employ simple parametric (t-test, either on raw or transformed data) or non-parametric (Mann-Whitney) tests as determined by the sample distributions of the outcome measures. Intention to treat and on-treatment analyses will be performed. Interaction effects will be examined with bilateral pre/post parameters. Secondary post-hoc, data driven analyses will also be conducted as required. Simple descriptive statistics will be used for all other analyses. Reasons for missing data will be recorded, and no imputation will be performed.

The anonymised dataset will be available on request to the PI for further analysis and comparison with other datasets.

Public and patient involvement

Two of the named investigators represent patient and public involvement in this study. They represent and consult with a larger, autonomous, PPI group, and both have considerable and varied expertise as PPI contributors to research. They have contributed to the overall research programme in which this study is nested. They have contributed to this protocol by requesting clarification and details of importance, particularly but not solely, related to the lay reader and patient.

Data management

Data management plan will be in line with the Nottingham University research data management policy (https://uniofnottm.sharepoint.com/sites/DMPCollection).

Ethical Approval

The protocol was approved by the East Midlands – Nottingham 2 Research Ethics Committee (IRAS number 292401. REC reference 21/EM/0037).

DISCUSSION

Our belief is that interventions sufficient to make a meaningful impact on independence and wellbeing after a fragility fracture will need to be multimodal. In frailty states the deficits and hence problems are multiple and it follows that multiple interventions will be required, on an individualised basis, to address a sufficient number of to alter outcome. The core of such an intervention package would include best existing care, including optimising resistance exercise and nutrition, but an enhanced package would include novel interventions such as neuromuscular electrical stimulation (NMES), whole body vibration therapy or anabolic drugs. Each intervention component needs to be demonstrated to be feasible in the population of interest before applied in a novel intervention package. We hope that this study will determine whether NMES is suitable to be used in such a novel intervention package. Further studies will be requires to test the feasibility of other novel

interventions in this study group and setting, before their synthesis in a novel multimodal package. Whilst the final trial of a multimodal intervention package will require meaningful clinical outcomes such as survival, independence, and mobility, we believe that potential candidate components need to demonstrate feasibility, acceptability, and efficacy at the biological level (such as improved muscle strength).

We acknowledge that this study will not be able to determine whether NMES improves clinical outcomes - partly because we will only stimulate one leg here yet obviously bilateral stimulation would be more suitable to optimise functional gains. We have chosen this method to determine whether NMES as we can deliver it will mimic the benefits seen in other uses of the technique at the muscular level. We acknowledge that further feasibility and acceptability research will be required when multimodal clinical treatment packages are developed further along the research pathway. We also acknowledge that this study will not examine the long-term community use of NMES, and further work will be necessary to do this since NMES could be an adjunct to rehabilitation in both the hospital and community phases.

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