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RESEARCH PAPER

Post-operative electrical muscle stimulation attenuates loss of muscle mass and function following major abdominal surgery in older adults: a split body randomised control trial

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Abstract

Introduction: Significant losses of muscle mass and function occur after major abdominal surgery. Neuromuscular electrical stimulation (NMES) has been shown to reduce muscle atrophy in some patient groups, but evidence in post-operative patients is limited. This study assesses the efficacy of NMES for attenuating muscle atrophy and functional declines following major abdominal surgery in older adults.
Methods: Fifteen patients undergoing open colorectal resection completed a split body randomised control trial. Patients' lower limbs were randomised to control (CON) or NMES (STIM). The STIM limb underwent 15 minutes of quadriceps NMES twice daily on post-operative days (PODs) 1–4. Ultrasound measurements of Vastus Lateralis cross-sectional area (CSA) and muscle thickness (MT) were made preoperatively and on POD 5, as was dynamometry to determine knee extensor strength (KES). Change in CSA was the primary outcome. All outcomes were statistically analysed using linear mixed models.
Results: NMES significantly reduced the loss of CSA (−2.52 versus −9.16%, $P < 0.001$), MT (−2.76 versus −8.145, $P = 0.001$) and KES (−10.35 versus −19.69%, $P = 0.03$) compared to CON. No adverse events occurred, and patients reported that NMES caused minimal or no discomfort and felt that ∼90-minutes of NMES daily would be tolerable.
Discussion: NMES reduces losses of muscle mass and function following major abdominal surgery, and as such, may be the promising tool for post-operative recovery. This is important in preventing long-term post-operative dependency, especially in the increasingly frail older patients undergoing major abdominal surgery. Further studies should establish the efficacy of bilateral NMES for improving patient-centred outcomes.

Keywords: neuromuscular electrical stimulation, muscle, surgery, atrophy, recovery, older people

Key points

- Major abdominal surgery causes significant acute muscle atrophy.
- Patients lose around 20% of knee extension strength in just 5 days after major abdominal surgery.
- Electrical muscle stimulation halves the loss of muscle mass and function in post-operative patients.

Introduction

Substantial losses of skeletal muscle mass and function occur after major gastrointestinal (GI) surgery due to the physiological insult of surgery [1], physical inactivity [2] and inadequate protein nutrition [2] in the post-operative period [3], with the greatest losses occurring in the first post-operative week [4]. In patients who had a colorectal resection, a 6.5% reduction in quadriceps cross-sectional area (CSA) was reported after 6 days [5], with similar losses reported following oesophagectomy (4.8%) [6]. Even greater losses are noted in patients admitted to an intensive treatment unit (ITU), with a median reduction of rectus femoris CSA of 12.5% over the first 7 days, rising to 17.7% by Day 10 [7]. Higher rates of post-operative muscle loss have been shown to be associated with an increased risk of post-operative complications [2], greater disease recurrence following cancer surgery [8] and worse survival [2, 6].

The majority of major abdominal surgery is performed in patients over 60 years of age [9, 10]. Older patients regain muscle function more slowly and less completely following major abdominal surgery [11], and surgery-related muscle loss is associated with declines in the muscle function important for independence [11], a slower return to normal activities and reduced quality of life [12]. Furthermore, the cumulative effect of repeated short bouts of muscle disuse in older age, such as those associated with surgery, may be a key factor in the development of sarcopenia [13], frailty and loss of independence [12], all of which incur burden to individuals, families and society [14] and are associated with numerous negative health outcomes [15].

Immobilisation, inflammation and starvation are recognised catabolic drivers, all of which are present in patients following major GI surgery [3]. Quantifying the relative contribution of each to the development of post-operative muscle atrophy is challenging, however, data from healthy volunteer studies of immobilisation show that disuse is likely a major contributor, with immobilisation alone shown to elicit a 3.5% loss of quadriceps CSA after 5 days [16], representing over half of the 6.5% loss seen in post-operative colorectal resection patients over a similar time frame [5].

Although increased contractile activity would seem the obvious answer to mitigate physiological declines associated with muscle disuse, it is clear that major abdominal surgery patients are unable to perform the level of physical activity required [17]. For example, following oesophagectomy, patients were sedentary for 96% of the first 5 days, taking just 86 (46–210) steps on the first post-operative day (POD) and only 474 (302–805) steps by POD 5 [18]. More strikingly, even in patients treated with an enhanced recovery after surgery (ERAS) protocol following colorectal resection, the median number of steps on POD 5 was <1,500, and in patients not following ERAS, steps were <500 [19]. Even in a patient cohort where >80% had laparoscopic resection, patients receiving standard care mobilised <500 steps per day on PODs 1–3, while patients receiving intense, twice-daily mobilisation support only achieved a maximum of 1,000 steps per day [20]. The most frequently cited factors preventing further mobilisation were haemodynamic instability [18], fatigue [19], pain [17] and attachment to drains, feeding apparatus and pumps [21]. As such, optimising muscle maintenance is not easily addressed. Studies in healthy older adults undergoing bed rest have shown that 2,000 steps per day are not enough to maintain skeletal muscle mass [22], therefore it is clear that post-operative patients are unable to perform enough physical activity to prevent muscle atrophy.

Neuromuscular electrical stimulation (NMES) is a technique of eliciting muscle contractions using electrical impulses without the requirement for voluntary contraction. Electrical impulses are transmitted transcutaneously and generate muscle fibre action potentials that would normally be transmitted via motor neurons to cause voluntary muscle contraction. In ITU patients, NMES has been shown to cause an increase in mammalian target of rapamycin (mTOR) phosphorylation, suggestive of its ability to activate the cell-signalling pathways associated with muscle protein synthesis (MPS) [23]. Similarly, in patients who had major abdominal surgery, NMES applied during recovery reduced markers of muscle protein breakdown [24]. Taken together, these findings suggest that NMES may be a pragmatic substitute for exercise in the post-operative period.

NMES has been shown to reduce muscle atrophy in immobilised healthy volunteers [25] and in patients following sporting [26] and spinal cord injuries [27]. In patients with chronic heart failure, NMES elicits comparable improvements in measures of fitness and strength to conventional exercise training-based cardiac rehabilitation [28–30]. There are, however, very few studies reporting the use of NMES following major abdominal surgery. Vinge *et al.* did report that NMES significantly reduced losses of skeletal muscle mass following colorectal resection, with associated improvements in MPS [5], but no assessment of muscle function was performed. In addition, while this study yielded promising data, it is a single study from >20 years ago before ERAS was widely introduced. Therefore, there remains a need for further studies to assess the ability of NMES to attenuate muscle mass and function in patients following major GI resection in current clinical settings.

The primary objective of this study was to assess the ability of NMES to attenuate Vastus Lateralis (VL) muscle mass losses following major colorectal resection in older adults. Secondary objectives included determining the impact of NMES on muscle function (knee extensor strength (KES)) and muscle architecture and characterising post-operative physical activity levels in this patient cohort. We also assessed the tolerability of NMES in this patient cohort to determine its viability as a treatment modality.

Methods

This split body randomised control trial was approved by the NHS Research Ethics Committee (20/EM/069, IRAS ID: 274048) and was registered with Clinicaltrials.gov (NCT04199936: https://clinicaltrials.gov/ct2/show/NCT04199936).

Adult patients scheduled to have major open colorectal resection, and those who met the study eligibility criteria based on their routine preoperative assessment were approached by the research team and provided with information regarding the study. Patients were eligible for inclusion if they: (i) were having open major colonic resection; (ii) had sufficient mobility to complete normal ERAS and (iii) were able to give informed consent. Patients were excluded if they had: (i) any pre-existing neuromuscular disease; (ii) a pacemaker, implantable cardiac defibrillator, implanted nerve simulator device or bilateral metal orthopaedic implants; (iii) inability to give informed consent; (iv) disability preventing normal mobilisation after surgery; (v) peripheral vascular disease, chronic kidney disease and chronic congestive cardiac failure or (vi) intubation for >24 hours post-operatively. Any patients who returned to theatre during the study period were excluded from the final analysis.

After eligibility was confirmed in person on the day of the patient's operation, written informed consent was obtained and baseline measurements were performed. All baseline measurements were repeated on POD 5 after 4 days of unilateral NMES.

Randomisation and blinding

After the baseline measurements were complete, patients' lower limbs were randomised using random permuted block sizes to act as control (CON) or undergo NMES (STIM). Due to the nature of the intervention, patients and the primary researcher were not blinded, however, interpretation of all ultrasound measurements, the primary outcome for this study, was checked by a blinded assessor.

Muscle mass assessment

To determine muscle CSA, the craniocaudal midpoint of the VL was identified as halfway between the greater trochanter of the femur and the midpoint of the patella. Medial and lateral boundaries of VL were identified at this level using B-mode ultrasound (Esaote, LA523/923 probes) and the intersection of the craniocaudal and medial-lateral midpoints were identified and marked using permanent ink. Marks were refreshed on each POD. Muscle CSA was measured at this point using video panoramic ultrasound as previously described [31]. Muscle architecture measures, including muscle thickness (MT), pennation angle (PA) and fascicle length (FL), were also made as previously described [32]. Ultrasound images were interpreted in ImageJ (NIHR, USA), with a mean value of three measures for each assessment at each timepoint used.

Muscle function assessment

To determine KES, patients were seated on the edge of the bed, with both knees flexed to 90°, and the bed was adjusted so that the patients' feet were hanging freely. A portable dynamometer (Lafayette Manual Muscle Tester, IN 47903, USA) offering static resistance was placed against the lower shin and patients were instructed to extend their knee against the device with maximum effort.

Muscle stimulation protocol

NMES was performed on the assigned leg twice each day on PODs 1–4 for 15 minutes per session with >3 hours between sessions. NMES was delivered using an NHS approved, CE-marked device (Premier Combo Plus, Med-Fit Ltd, UK) using two large (7.5 × 13 cm) electrodes placed proximally and distally over the lateral quadriceps. NMES was delivered at a frequency of 30 Hz and delivered in a 1 second on, 1 second off pattern. Amplitude settings were determined prior to baseline measurements and were set at the minimum level required to produce both visible contractile activity in the muscle and involuntary movement at the knee joint with patients seated, knees flexed at 90° and feet hanging freely. Mean (SD) amplitude was 36.5 (±6.8) mAmp.

Physical activity levels and patient feedback

Physical activity levels were recorded using a self-report questionnaire (Supplementary Appendix 2). Distance walked was measured by a member of the research team after patients identified landmarks to which they had mobilised. Step counts were derived from the distance measured, using a conversion factor of 1.439 steps per metre [33]. After the final NMES session, patients were asked to rate the level of discomfort elicited by NMES on a text-based Likert Scale and to state the maximum duration of NMES per day they considered tolerable.

Statistical analysis

Based on the split body design of this randomised control trial, a sample size of 12 patients was determined to have >80% power to detect a mean difference in VL CSA change of 5cm^2 based on a pooled SD of change of 2.07 cm^2. Distribution of data was tested using the Kolmogorov–Smirnov test, with normally distributed data expressed as mean (±SD) and non-normally distributed data as median (IQR). If only one measurement was compared, paired *t*-tests or Wilcoxon signed rank was used as appropriate. To account for the structure of the data, we analysed the outcomes using linear mixed models. Times (pre and post) were included with random intercepts and slopes and each leg was nested within individuals. Outcomes are reported as the interaction between time and leg. Where possible, an unstructured variance–covariance structure was used for the random effects. Results are presented as mean differences (MD) with 95% confidence intervals (CIs) and *P*-values.

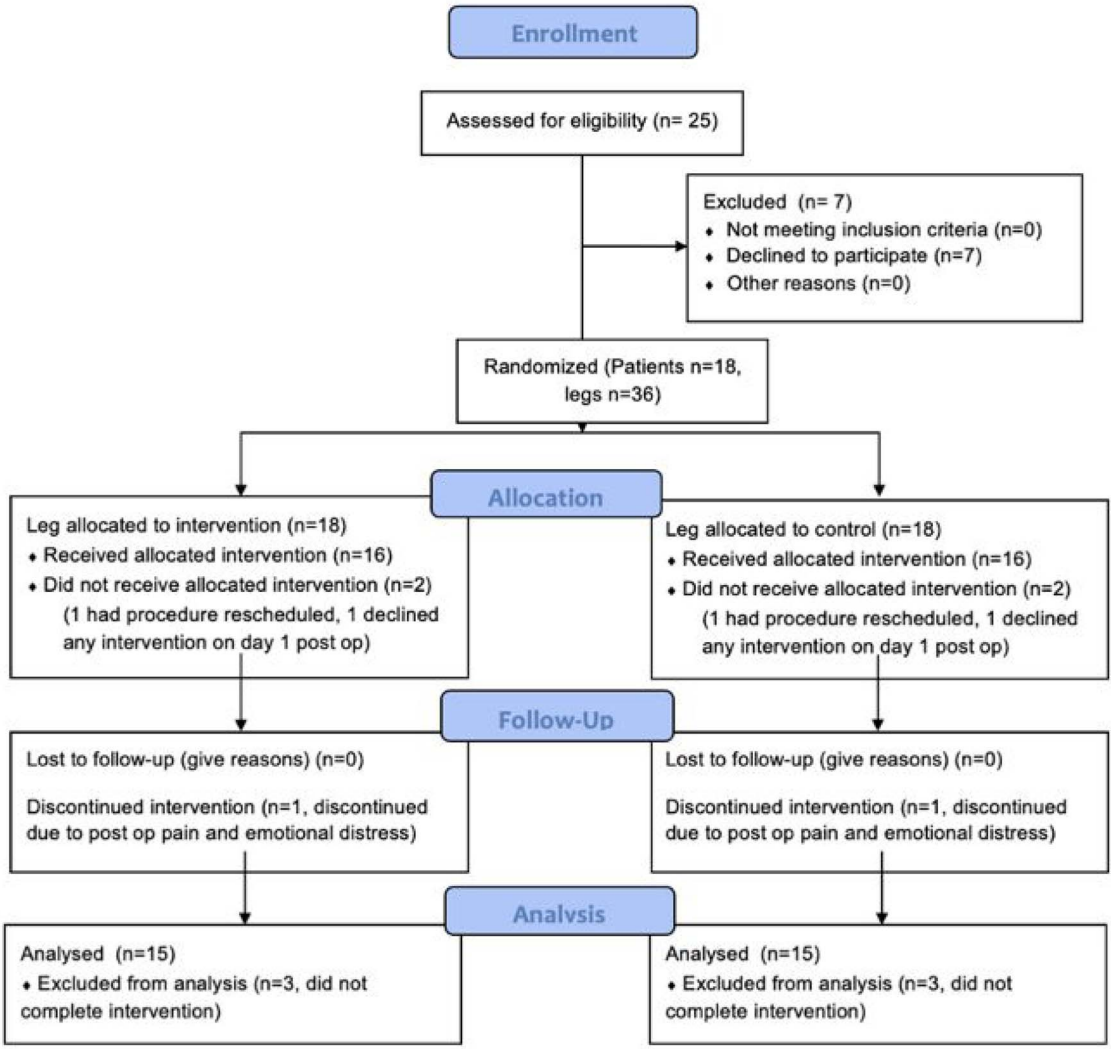

Figure 1. CONSORT diagram.

We regarded $P < 0.05$ as statistically significant. All analyses were conducted using Stata Version 16.1.

Results

Eighteen patients were recruited to take part in the study and were randomised, with 15 patients completing the study (Figure 1). No patients withdrew because of NMES and no adverse events were reported. Patient demographics for those who completed the study are summarised in Table 1. All patients had open major colonic resection; 13 for rectal cancer, 1 for hepatic flexure cancer in the presence of ulcerative colitis and 1 for stricturing diverticular disease.

Muscle mass, function and architecture

The was no significant difference between VL CSA of the CON (17.18cm^2 (±2.85)) and STIM (16.48cm^2 (±2.56)) legs preoperatively ($P = 0.16$). By POD 5, VL CSA in the CON limb had decreased by 1.60 cm^2 (±0.54) to 15.58 cm^2 (±2.43), representing a loss of 9.16% (±2.0). VL CSA in the STIM leg decreased to 16.06 cm^2 (±2.48) by POD 5, a change of −0.42cm^2 (±0.2), representing a loss of 2.52% (±1.07). CSA loss in the CON leg was significantly greater than in the STIM leg ($P < 0.001$; Figure 2).

Table 1. Patient demographics.

N	15
Male:female	4:1
Age (years)	66 (±5.9)
BMI (kg/m^2)	28 (±4.0)

The was no significant difference between VL MT of the CON (2.08 cm (±0.30)) and STIM (2.06 cm (±0.25)) legs preoperatively ($P = 0.74$). By POD 5, VL MT in the CON limb had decreased by 0.17 cm (±0.13) to 1.91 cm (±0.26) (8.14% (±5.93) loss). VL MT in the STIM leg decreased by 0.05 cm (±0.06) to 2.01 cm (±0.28) by POD 5 (2.76% (±3.56) loss). The losses in the CON leg were significantly greater than in the STIM leg ($P < 0.001$; Figure 3). There was no difference between legs pre

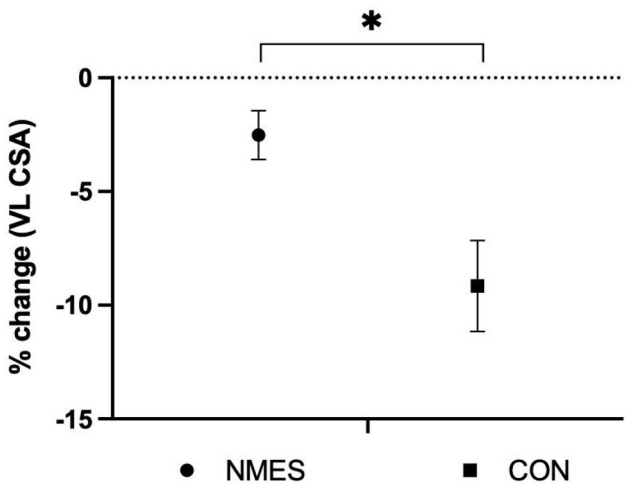

Figure 2. Percentage change in VL muscle CSA from baseline to POD5 with and without NMES. * = $P < 0.05$. MD 1.18 (95% CI: 0.75–1.61; $P < 0.001$).

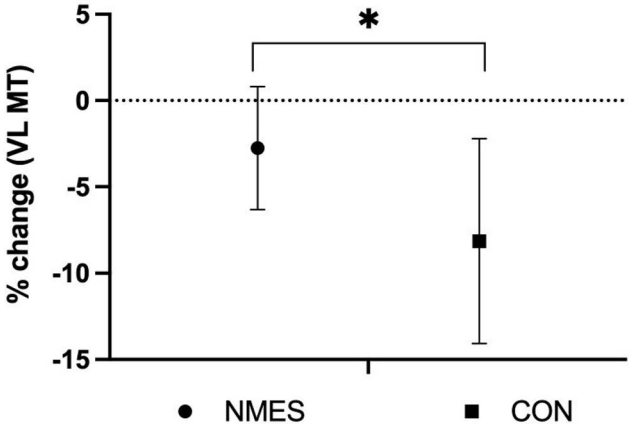

Figure 3. Percentage change in VL MT from baseline to POD5 with and without NMES. * = $P < 0.05$. MD 0.12 (95% CI: 0.04–0.2; $P = 0.001$).

or post-operatively and no difference in change between legs for FL or PA (Supplementary Appendix 2).

There was no significant difference in KES between the CON (44.44lbs (±8.15)) and STIM (44.7lbs (±7.26)) legs preoperatively ($P = 0.93$). By POD 5, KES in the CON limb had decreased by −9.30 lbs (±6.72) to 35.13 lbs (±6.56) (−19.69% (±12.91)). STIM leg KES decreased by −4.82 lbs (±4.65) to 39.88 lbs (±6.71) (−10.35% (±8.98) by POD 5. The decrease in the CON leg was significantly greater than in the STIM leg ($P = 0.03$; Figure 4).

Post-operative physical activity

Although patients spent the majority of PODs 1–4 in bed, time spent in bed was significantly less on POD 3 (18.7 hours (±4.2)) and POD 4 (18.25 hours (±4.9)) compared to POD 1 (23 hours (19.8 (±3.5)), both $P < 0.01$). Numerically, time spent mobilising (15.45 (±9.3) to 26.36 (±21.1) minutes), $P = 0.06$) and distance mobilised increased (30.0 m (±23.6) to 93.6 m (±166.6), $P = 0.11$), but these changes did not reach statistical significance.

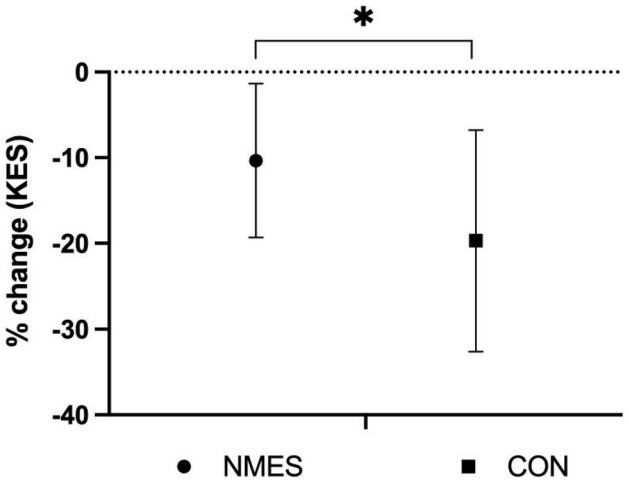

Figure 4. Percentage change in KES from baseline to POD5 with and without NMES. * = $P < 0.05$. MD 4.48 (95% CI: 0.00–8.97; $P = 0.03$).

Patient preferences

Overall, 26.7% of patients stated that NMES caused no discomfort, while the remaining 73.3% reported it to cause slight discomfort. The median maximum time patients felt NMES would be tolerable for was 88.75 minutes per day, with answers ranging from 45 to 240 minutes.

Discussion

In this study, NMES significantly attenuated the loss of VL CSA and MT and KES following open colorectal resection in older adults. To our knowledge, this is the first time the effects of NMES on muscle function following major abdominal surgery have been reported and the first time the effects on muscle mass have been reported in the current clinical environment (i.e. since the implementation of ERAS).

Although there is no study of NMES after abdominal surgery in the current era, it is known that NMES reduces losses of muscle mass [34] and function [35] in ITU patients and loss of muscle function following cardiac surgery [36]. Our results, along with those of previous studies, suggest that NMES may represent a useful therapy to enhance ERAS regimes for decreasing muscle loss after surgery.

There is variability in reports of the efficacy of NMES on muscle 'health', with some meta-analyses reporting inconclusive evidence for its benefit in patients following, for example, orthopaedic surgery [37] and ITU admission [38]. This may be due to the significant heterogeneity in the

administration of NMES observed across and indeed sometimes within studies [37, 39]. Variations include the length of time NMES is applied for, the amplitude, frequency and/or pulse width of the stimulation within in a session and the frequency of sessions. Furthermore, the stimulation site may also affect NMES effectiveness, with recent work showing that peripheral nerve stimulation recruits from a wider pool of motor units that NMES [40].

Dose–response studies are required to further our proof-of-concept finding and to establish the optimum NMES delivery protocol to prevent losses of muscle mass and function in healthy immobilised, critically unwell and post-operative patients, each of whom will likely have differing physiological responses to and tolerance of NMES. Encouragingly, in this study, our NMES protocol was well tolerated, causing either mild or no discomfort, and all patients felt they would be able to tolerate longer periods. This, along with the feasibility to collect and analyse data related to NMES efficacy in this patient population, is an important consideration if NMES is to be developed into an accepted clinical therapy.

The reductions in VL CSA and MT observed in our control limb are consistent with those previously described following major abdominal surgery. Although, numerically, the losses in this study appear to be larger than those previously reported, this may be due to the differing disuse atrophy susceptibility of individual muscles [32], with previous studies often reporting whole-body [6], psoas [41] or grouped quadriceps [5] changes. Muscle function decreases in the control limb are also in keeping with previous studies showing loss of muscle strength [19] and a delay in return to normal walking activities [20] following major abdominal surgery. The greater loss of muscle function compared to muscle mass as seen in this study has been previously described with disuse [42] and may be due to a decline in muscle quality as well as quantity [42, 43]. In the latest definition of sarcopenia from the European Working Group on Sarcopenia in Older People [44], muscle quality is described as 'micro- and macroscopic aspects of muscle architecture and composition', and although we did not see any changes in our muscle architecture parameters (FL and PA) in either leg, other aspects of muscle quality such as myosteatosis [45] and neuromuscular connectivity [46] may have contributed to the attenuation of functional declines observed with NMES. The underlying mechanisms of NMES-induced preservation of muscle mass and function in post-operative patients' need further exploration.

Despite this study being conducted on a background of ERAS, patients in our study had low levels of post-operative mobility, walking an average of <100 m by POD 4 after surgery. As there is insufficient evidence to support specific values [47], ERAS guidelines do not set any daily recommended activity level targets, leading to wide variability in practice. For example, ERAS patient information from one UK NHS trust advises a target of 250 steps on POD 1 increasing to 1,250 steps on POD 4 [48], a target not met by the patients in this study. Our results are similar to a number of other studies which have also shown poor overall mobility following major abdominal surgery [17–20, 49]. This observation of low levels of post-operative mobility further supports the potential benefit of NMES to somewhat compensate for challenges in full adherence to ERAS.

While the ability of NMES to significantly decrease the loss of muscle mass and function in post-operative patients demonstrated in this study is encouraging, it is recognised that the current results have several limitations. Although the VL is widely recognised as functionally important for locomotion and other activities of daily living, to bring the most meaningful benefit to patients, it may be more beneficial stimulate all the major muscle groups involved in locomotion. However, the effectiveness of NMES in other muscle groups, which may have different fibre composition and motor unit structure will need to be investigated.

That this intervention could easily be incorporated into the current post-operative clinical setting via self-administration, or with minimal staffing support, is promising for future clinical translation. However, while we demonstrated the effectiveness of NMES in reducing losses of KES, the ability of post-operative NMES to preserve whole-leg muscle function, including those associated with independence maintenance and activities of daily living (e.g. standing, walking and balance) and/or clinical outcomes (i.e. length of stay), remains to be determined.

In conclusion, this study has demonstrated the ability of NMES to attenuate mass and functional losses in the functionally important quadriceps muscle. Further studies are now required to optimise NMES, ideally without the need for individual assessments before the intervention is delivered and to establish the practicality of bilateral whole-leg NMES in older patients following major abdominal surgery.

Supplementary data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

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