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Neuromuscular Electrical Stimulation Preserves Muscle Strength Early after Total Knee Arthroplasty: Effects on Muscle Fiber Size

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Abstract

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AUTHOR CONTRIBUTIONS STATEMENT

Victor Cheuy, Jennifer Stevens-Lapsley, Nathaniel Nelms and Michael Toth conceived the study. Victor Cheuy, Michael Dayton, Craig Hogan, Jeremy Graber, and Jennifer Stevens-Lapsley were responsible for data collection. Bradley Anair, Thomas Voigt, and Michael Toth were responsible for processing and data analyses. All authors edited the manuscript. All authors have read and approved the final submitted manuscript.

Loss of quadriceps strength after total knee arthroplasty (TKA) is most pronounced acutely but persists long-term, negatively impacting physical function in daily activities. Neuromuscular electrical stimulation (NMES) early after surgery is an effective adjuvant to standard of care rehabilitation (SOC) for attenuating strength loss following TKA, but the mechanisms whereby NMES maintains strength are unclear. This work aimed to determine the effects of early NMES on quadriceps strength and skeletal muscle fiber size two weeks after TKA compared to SOC. Patients scheduled for primary, unilateral TKA were enrolled and randomized into SOC (n=9) or NMES plus SOC (n=10) groups. NMES was started within 48 hours of TKA, with 45-minute sessions twice a day for two weeks. Isometric quadriceps strength was assessed preoperatively and two weeks following TKA. Vastus lateralis muscle biopsies of the involved leg were performed at the same time points and immunohistochemistry conducted to assess muscle fiber cross-sectional area and distinguish fiber types. Groups did not differ in age, BMI, sex distribution, or preoperative strength. Both groups got weaker postoperatively, but the NMES group had higher normalized strength. After two weeks, the group receiving NMES and SOC had significantly greater MHC IIA and MHC IIA/IIX fiber size compared to SOC alone, with no group differences in MHC I fiber size. These results suggest that NMES mitigates early muscle weakness following TKA, in part, via effects on fast-twitch, type II muscle fiber size. This investigation advances our understanding of how adjuvant, early postoperative NMES aids muscle strength recovery.

Keywords

NMES; arthroplasty; quadriceps; strength; fiber

INTRODUCTION

Over 700,000 total knee arthroplasties (TKAs) are performed annually in the United States to alleviate the pain and disability associated with knee osteoarthritis (OA)[1], and this number will increase four-fold by 2040.[2] The recovery of muscle strength and physical function after TKA remains a major challenge. Patients are often satisfied with the postoperative improvement in pain, but they rarely regain function comparable to age-matched cohorts without knee OA.[3] These functional deficits are attributable to a combination of pre-existing quadriceps weakness associated with knee OA, the surgical trauma of TKA, and age-related limitations in the recovery of muscle function.[4–6] Reduced quadriceps force production typically persists indefinitely after TKA[7], predisposing this clinical population to greater disability later in life.

An NIH consensus statement on TKAs stated “the use of rehabilitation services is perhaps the most understudied aspect of the perioperative management of patients [with TKA]”.[8] Several investigations have demonstrated a deficit of up to 60% in quadriceps strength as early as one month after surgery compared to preoperative values, largely attributable to impaired neuromuscular activation and atrophy.[5] Rehabilitation has the potential to address the deleterious effect of knee OA and TKA on the muscle morphology and force-generating ability of the quadriceps in older individuals.

Neuromuscular electrical stimulation (NMES) offers an approach to mitigate quadriceps weakness and restore quadriceps muscle function more effectively.[9–13] Starting NMES immediately following TKA, Avramidis et al.[14] found greater walking speeds after 6 weeks of treatment compared with patients who did not receive NMES, with benefits persisting after NMES was discontinued. Stevens-Lapsley et al.[12] evaluated the efficacy of early NMES (within 48 hours after TKA) applied to the quadriceps for 6 weeks as an adjuvant therapy to standard rehabilitation in a randomized controlled trial. In this study, NMES attenuated quadriceps strength loss and improved functional performance and self-reported function after TKA. Clinically meaningful effects were apparent and most pronounced early after surgery (i.e., 3.5 weeks following TKA). The mechanism behind these early improvements in muscle function with NMES, however, are unclear.

To date, no studies have directly investigated the mechanism of action of early NMES intervention after TKA. While NMES as an adjunct to standard of care (SOC) postoperative rehabilitation is thought to improve muscle strength by increasing neuromuscular activation, its effect on intrinsic skeletal muscle properties, such as muscle size, is unclear. Measurement of the quadriceps muscle at the cellular level provides a more rigorous index of muscle size to elucidate if the unbiased muscle fiber activation provided by NMES results in the preservation or hypertrophy of certain fiber types, particularly fast-twitch muscle fibers, which have a greater responsiveness to repeated muscle contractions and are strong determinants of muscle power output. The purpose of this study was to determine the effects of NMES on quadriceps muscle size at the cellular (i.e., single muscle fiber) level and quadriceps strength two weeks after TKA compared to SOC.

METHODS

Study Design

This randomized controlled study was performed at the University of Colorado Anschutz Medical Campus (ClinicalTrials.gov registration identifier: NCT02281877). All testing was completed at the University of Colorado Hospital and the Clinical Translational Research Center. The study was approved by the Colorado Multiple Institutional Review Board and informed consent was obtained from all participants.

Participants

Recruitment occurred from 2017 to 2020. Inclusion criteria were 50 to 75 years of age, diagnosis of osteoarthritis, and scheduled for a primary unilateral TKA at University of Colorado Hospital. Exclusion criteria were neurological (e.g., Parkinson's Disease, stroke) or cardiovascular problems that significantly limited function, BMI > 35 kg/m^2, uncontrolled diabetes, hypertension, or thyroid disease, presence of contralateral knee osteoarthritis (i.e., self-reported non-surgical knee pain > 4 out of 10 with walking or stair climbing)[12,15–17], implanted pacemaker or ICD, current anticoagulant or testosterone therapy, pregnancy, and any other unstable lower extremity orthopedic conditions.

Treatment

Patients were randomized to one of two treatment groups: NMES or SOC. All patients received standard physical therapy for the progression of prescribed exercises. Patients recorded their physical therapy exercises daily in a log to document frequency and exercise progression. Patients randomized to the NMES group also received NMES treatment via an Empi 300PV stimulator (Empi Inc, DJO Global company, USA), starting post-operative day two. Stimulation parameters were set to 50 Hz frequency, 400 μs pulse duration, symmetrical biphasic waveform, and a 25% duty cycle. An initial orientation session to NMES, including education for independent home use, was provided after TKA immediately followed by initiation of treatment. Participants used NMES twice per day, 45 minutes per session, for 14 days. The intensity was set to the maximal tolerable intensity during each session, and participants were directed to increase the intensity as tolerated. During treatment, the lower limb was secured by Velcro straps to a stable chair to approximate 85 degrees of hip flexion and 60 degrees of knee flexion.[12] Straps were individually pre-adjusted to the necessary length for each participant to stop at 60 degrees of flexion as measured by goniometer. Home visits by study personnel were also conducted to ensure fidelity given chair-to-chair differences. Self-adherent, flexible rectangular electrodes were placed on the distal medial and proximal lateral portions of the anterior thigh and marked to ensure consistent reapplication by the participant.

Biopsies

Muscle biopsies were acquired under sterile conditions from the vastus lateralis of the involved leg in the operating room immediately prior to TKA and two weeks after TKA (range 15–17 days to accommodate logistical considerations). All muscle biopsies were performed by a surgeon or physician's assistant using similar incision sites at each time point with previously published methods that are well-tolerated in older adults.[10,18] Briefly, intramuscular lidocaine was administered to the dermis where the incision was made. Upon ensuring the area was anaesthetized, a small incision was made using a sterile scalpel. A sterilized (i.e., by autoclave) biopsy needle was passed into the muscle in order to obtain a small piece of muscle tissue. A piece of tissue was frozen in embedding medium (OCT; Sakura, Torrance, CA) and stored at −80°C. To reduce the risk of infection and bleeding, triple antibiotic ointment was used on the incision and the wound was covered with Steri-Strips and bandaged with elastic wrap.

Immunohistochemistry

Muscle fiber size was assessed by immunohistochemistry, as detailed previously.[19] Briefly, muscle tissue cross sections were cut, dried, rehydrated and incubated with antibodies for MHC I [Developmental Studies Hybridoma Bank (DSHB) BA-D5; 1:100], MHC IIA (DSHB SC-71; 1:600), and MHC IIX (DSHB 6H1; 1:50) in PBS containing 1% bovine serum albumin (BSA) and 0.1% Triton X-100 overnight. After washing, secondary antibodies (all Thermo Fisher: goat anti-mouse Alexa Fluor 646 A-21242; goat anti-mouse Alexa Fluor 488 A-21121; goat anti-mouse Alexa Fluor 568 A-21043; all 1:500) were applied for 1 h, followed by postfixing with methanol. Image acquisition was performed with an Olympus BX51 microscope (Olympus America, Center Valley, PA) at ×20, with

analysis using ImageJ. Minimum Feret's diameter measurements were obtained for each fiber to control for myofiber orientation and cutting artifact.[20]

Quadriceps Strength

Baseline isometric quadriceps strength testing occurred at least three days before TKA; post-operative strength testing at the two-week follow-up time point occurred the same day and immediately following the muscle biopsy. Briefly, patients were seated and stabilized in a HUMAC NORM (Computer Sports Medicine Incorporated, USA) electromechanical dynamometer with their knee flexed to 60 degrees. After proper warm up, patients were asked to perform maximum voluntary isometric contractions of their quadriceps while receiving verbal reinforcement until two attempts were within 5% torque output of each other. The trial with the largest maximal volitional isometric force output was then normalized to each participant's body weight (kg) and used for data analysis. Testers were not blinded to group assignment because of staffing limitations, although standardized methods were used to eliminate bias with testing.

Statistical Analyses

Baseline characteristics of the treatment groups were compared using two-sample t tests for continuous measures and a chi-square test for independent proportions for categorical measures. Treatment effects were modeled using analysis of covariance (ANCOVA), with follow-up in normalized strength as the dependent variable and baseline strength as a covariate, with group (SOC, NMES) as the between-subjects factor. For muscle fiber size, mixed-model ANOVA was used, with group as the between-subjects factor and time (baseline, follow-up) as the within-subjects factor. If significant group x time interaction effects were observed, differences between groups were identified using simple contrasts. If measures were not normally distributed, log transformations were performed before analysis. SPSS 27 (IBM, USA) was used for ANCOVA analysis and SAS 9.4 (SAS Institute, Cary, NC) for mixed model analyses. Analyses did not adjust for nonadherence to NMES. A two-sided alpha level of .05 was designated for statistical significance.

RESULTS

Groups did not differ in age, sex distribution, height, weight, or BMI (Table 1). Seven out of the ten NMES participants provided records of their adherence. Of those seven, adherence to the prescribed number of NMES sessions was 79 ± 20% (range: 46 – 100%) and to the total amount of NMES device use time (in minutes) was 74 ± 24% (range: 44 – 100%).

While normalized quadriceps strength decreased in both groups, as expected, the NMES group had a 39% higher normalized quadriceps strength at follow-up assessment [mean (SE): 0.68 (0.06) vs 0.49 (0.06) N-m/kg, p = .039] (Table 2).

Treatment effects on muscle fiber size are shown in Figure 1. No group-by-time (GxT) interaction effect was found for MHC I fibers (p = .581). A GxT interaction effect (p = .005) was found for MHC IIA fibers, due to an increase in the minimum Feret's diameter over time in the NMES group (p = .005) and no change (p = .139) in the SOC group. Similarly, a GxT interaction effect (p = .002) was found for MHC IIA/IIX fibers, secondary to increased

fiber diameter in the NMES group (p = .005) and decreased diameter in the SOC group (p = .035).

DISCUSSION

To our knowledge, this is the first study to provide mechanistic data in the setting of a randomized controlled study that demonstrates the ability of NMES to beneficially modify muscle fiber size in the early postoperative period after TKA. Our results show that NMES attenuates loss of quadriceps muscle strength as early as two weeks after surgery and this effect is accompanied by greater muscle fiber size.

The reduction in quadriceps strength in the SOC group (−62%) is comparable to what we and others have shown over the first 3–4 weeks after TKA[5,12,21], confirming that a large portion of the strength loss occurs early after surgery. While there is no agreed-upon minimum clinically important difference in quadriceps strength outcomes for patients undergoing TKA, the attenuation of muscle weakness by NMES at the two-week follow-up after TKA was similar to our observations at 3.5 weeks following TKA in a prior study[12], and exceeded previously published small-to-medium effect sizes at three weeks following TKA (i.e., reported effect sizes are equivalent to a normalized strength value change of approximately 0.15 N-m/kg).[22] These results reinforce a considerable body of data suggesting that NMES is an effective adjunct to SOC postoperative rehabilitation to preserve quadriceps strength.[11]

The beneficial effect of NMES on whole muscle strength after surgery may relate to its use so early post-surgery (within 48 hours), but also to its dosing. Forty-five minute sessions twice per day is more than triple the number of contractions reported in previous studies[12], but in line with recent treatment algorithm recommendations.[23] It is recommended to employ an initial high-intensity, high-volume phase of NMES therapy for the first three weeks after surgery to maximize exposure when neuromuscular activation failure is greatest.[23] A second three-week phase of high-intensity and low-volume NMES therapy is then recommended if patients show an adequate response to phase one. Taken together, the results of this study and previous literature support NMES as an adjuvant rehabilitation modality to improve muscle strength, and promote lasting functional recovery after TKA.

The ability of NMES to preserve quadriceps muscle strength has been attributed primarily to its ability to maintain neuromuscular activation[24], but most studies evaluating its effects on muscle size have used whole muscle imaging techniques, with only one study, to our knowledge, evaluating its effects on skeletal muscle size at the cellular level.[25] This is an important distinction because whole muscle assessments may be confounded in the early post-surgical period by fluid infiltration related to surgical trauma and/or inflammation and, in turn, may underestimate muscle atrophy.[26] Caution is required, therefore, in interpreting whole muscle size data and we suggest cellular level measures as a more rigorous index of muscle size in the early postoperative period. Our data show that NMES elicited a mild hypertrophic response in MHC IIA and IIA/IIX fibers, whereas TKA was associated with atrophy of IIA/IIX fibers in the SOC group. While NMES has historically been thought to preferentially activate fast motor units[27], it is now generally accepted that NMES does not

bias toward activation of a specific fiber type.[28,29] Instead, the most likely explanation for the predominant effect of NMES on fast-twitch, MHC II fibers is their greater responsiveness to repeated muscle contractions, such as with resistance training.[30–32] In contrast, we found no effects on slow-twitch, MHC I fibers. Our results differ slightly from the one study that examined effects of NMES on muscle fiber size after TKA. In this study, TKA was associated with profound atrophy of histochemically-defined slow-twitch, Type I and fast-twitch, Type II, fibers (−36% to −45%, respectively) and NMES largely prevented these reductions (to 8% and 9%, respectively).[25] Similar effects of NMES to prevent fiber atrophy were observed after anterior cruciate ligament reconstruction.[33] Importantly, both of these studies were conducted ~30 years ago when postoperative management included extended hospital stays and, in turn, greater disuse atrophy. Regardless of reasons for differences between studies, our results suggest that NMES-induced preservation or increase of fast-twitch MHC II muscle fiber size may contribute to its effect to sustain quadriceps muscle strength early post-surgery.

An important strength of this study was the measurement of the quadriceps muscle at the fiber level to evaluate the effects of NMES in the early post-surgical period. However, there are limitations. Analyses were limited to fibers expressing MHC I, MHC IIA, and MHC IIA/IIX, as other fiber types (MHC I/IIA, I/IIA/IIX, and IIX) are typically too few to permit analysis in humans.[34] Patient bias was possible as knowledge of group randomization was unavoidable and the control group did not receive NMES stimulators; however, the large majority of NMES studies do not include a sham treatment[12,35], although recent studies utilizing a shame control have shown similar benefits of NMES on muscle fiber size after anterior cruciate ligament reconstruction.[36] Investigators who performed the quadriceps assessments were not blinded, but standardized testing methods were used to reduce bias. Additionally, we did not assess neuromuscular activation failure, which is well described following TKA, to assess the contribution of neural versus muscle factors to quadriceps weakness. Generally speaking, the mechanisms underlying quadriceps weakness following TKA can be conceptualized into 1) muscular (e.g., decreased muscle mass) or 2) neural (e.g., impaired neuromuscular activation) in nature[37], with the muscular component contributing most to the prolonged strength deficits observed years into the recovery process compared to healthy older adults.[11] While we have shown that NMES achieves its clinical benefit, in part, by improving neuromuscular activation,[12] to our knowledge, the current study represents the first effort to evaluate the effects of NMES on quadriceps muscle fiber size early (i.e., less than one month) after TKA. Finally, lower BMI may amplify NMES treatment as less thigh adiposity results in less impedance. The study groups had lower mean BMIs than the reported national average of the TKA population at 32.9 kg/m^2.[38] Therefore, generalizability to patients with a higher BMI is more limited.

CONCLUSION

Our results suggest that NMES mitigates early muscle weakness following TKA, in part, via effects on type II muscle fiber size. This investigation improves our understanding of how early adjuvant NMES aids in attenuating loss of quadriceps muscle strength and improving functional performance following TKA.

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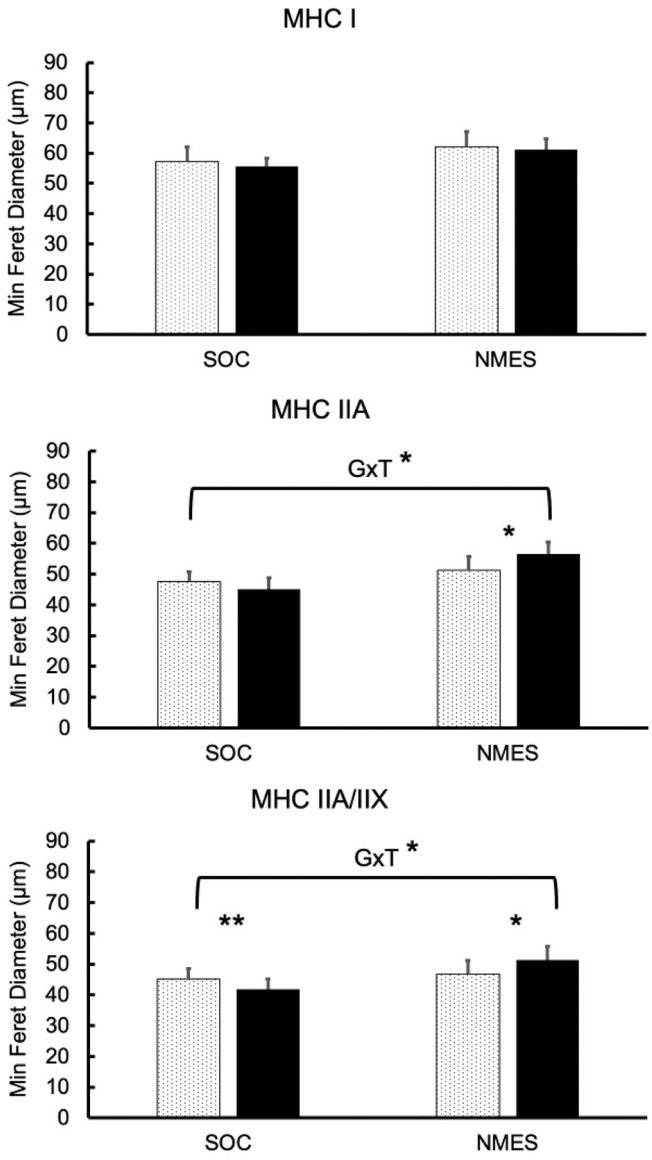

FIGURE 1.

Minimum Feret's diameter for myosin heavy chain (MHC) I, IIA, and IIA/IIX fibers in patients randomized to SOC control and NMES groups at baseline (pattern bars) and two-week follow-up (solid bars). Group-by-time (GxT) interaction effects are indicated. Pairwise analysis of differences between groups when significant GxT interactions were found are indicated above the bars. Data presented as means ± SE. *$p < .01$; **$p < .05$.

TABLE 1.

Baseline characteristics of the SOC and NMES Groups

Variable	SOC (n = 9)	NMES (n = 10)	P
Age (years)	65 (6)	68 (4)	.21
Sex (n)	6 F, 3 M	4 F, 6 M	.25
Height (cm)	173.7 (13.5)	173.2 (12.2)	.92
Weight (kg)	78.7 (19.3)	80.7 (17.3)	.81
BMI (kg/m2)	25.8 (3.6)	26.8 (4.6)	.61

Data presented as mean (SD)

TABLE 2

Normalized Quadriceps Strength of the SOC and NMES Groups

Time Point	SOC (n = 9)	NMES (n = 10)	p
Unadjusted			
Baseline	1.30 (0.28)	1.34 (0.56)	
Follow-up	0.49 (0.09)	0.68 (0.07)	
Adjusted[*]			
Follow-up	0.49 (0.06)	0.68 (0.06)	.04

Data presented as mean (SE); units are N-m/kg;

[*] covariate is baseline value.

Note that the reason that the Adjusted group means did not change is because the covariate (baseline strength) had no effect.