A Clinical Trial of Neuromuscular Electrical Stimulation in Improving Quadriceps Muscle Strength and Activation Among Women With Mild and Moderate Osteoarthritis

Riann M. Palmieri-Smith, Abbey C. Thomas, Carrie Karvonen-Gutierrez, MaryFran Sowers

Background. Neuromuscular electrical stimulation (NMES) has demonstrated efficacy in improving quadriceps muscle strength (force-generating capacity) and activation following knee replacement and ligamentous reconstruction. Yet, data are lacking to establish the efficacy of NMES in people with evidence of early radiographic osteoarthritis.

Objective. The purpose of this study was to determine whether NMES is capable of improving quadriceps muscle strength and activation in women with mild and moderate knee osteoarthritis.

Design. This study was a randomized controlled trial.

Methods. Thirty women with radiographic evidence of mild or moderate knee osteoarthritis were randomly assigned to receive either no treatment (standard of care) or NMES treatments 3 times per week for 4 weeks. The effects of NMES on quadriceps muscle strength and activation were evaluated upon study enrollment, as well as at 5 and 16 weeks after study enrollment, which represent 1 and 12 weeks after cessation of NMES among the treated participants. The Western Ontario and McMaster Universities Osteoarthritis Index and a 40-foot (12.19-m) walk test were used at each testing session.

Results. Improvements in quadriceps muscle strength or activation were not realized for the women in the intervention group. Quadriceps muscle strength and activation were similar across testing sessions for both groups.

Limitations. Women were enrolled based on radiographic evidence of osteoarthritis, not symptomatic osteoarthritis, which could have contributed to our null finding. A type II statistical error may have been committed despite an *a priori* power calculation. The assessor and the patients were not blinded to group assignment, which may have introduced bias into the study.

Conclusions. Four weeks of NMES delivered to women with mild and moderate osteoarthritis and mild strength deficits was insufficient to induce gains in quadriceps muscle strength or activation. Future research is needed to examine the dose-response relationship for NMES in people with early radiographic evidence of osteoarthritis.

R.M. Palmieri-Smith, PhD, ATC, is Associate Professor, School of Kinesiology, University of Michigan, 4745G CCRB, 401 Washtenaw Ave, Ann Arbor, MI 48109 (USA), and Bone & Joint Injury Prevention & Rehabilitation Center, University of Michigan. Address all correspondence to Dr Palmieri-Smith at: riannp@umich.edu.

A.C. Thomas, MEd, ATC, is a doctoral candidate in the School of Kinesiology, University of Michigan.

C. Karvonen-Gutierrez, MPH, is Research Analyst/Epidemiologist and doctoral student, Department of Epidemiology, School of Public Health, University of Michigan, and Center for Integrated Approaches to Complex Diseases, School of Public Health, University of Michigan.

M.F. Sowers, PhD, is John G. Searle Professor of Public Health and Professor of Epidemiology, Department of Epidemiology, School of Public Health, University of Michigan, and Center for Integrated Approaches to Complex Diseases, School of Public Health, University of Michigan.

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Tibiofemoral osteoarthritis (OA) is the most common cause of chronic disability in the United States[1] and is the most frequent indication for total knee arthroplasty.[2] No cure exists for OA, and current treatment approaches are quite limited, with surgery becoming an increasingly frequent endpoint. In recent years, OA has been identified in adults at younger ages,[3] accentuating the need to develop interventions effective in restoring normal function and capable of retaining or slowing the process of joint degeneration. If effective interventions are not identified, joint replacement surgery will be needed at earlier ages to maintain mobility and quality of life.

Quadriceps muscle weakness is commonly associated with tibiofemoral OA,[4–7] is linked with physical disability,[5] and may play a role in disease pathogenesis.[8] Quadriceps muscle strength (force-generating capacity) appears to be highly related to functional performance,[9] and minimizing weakness has been shown to result in clinical or mechanical improvements in a variety of populations.[10–12] Enhancing quadriceps muscle strength, therefore, is considered to be of benefit, as it may improve quality of life. Research is limited on the benefits of quadriceps muscle strengthening early in the OA disease process, as most investigations have targeted people in the end stages of the disease or following total knee arthroplasty.[11] Improving quadriceps muscle strength during the early stages of the disease process may prove beneficial, not only for maximizing function and minimizing pain but also for delaying the rate of disease progression. Furthermore, enhancing quadriceps muscle strength in people with radiographic evidence of the disease who are without symptoms may contribute to preventing the onset of symptomatic OA.[13]

Neuromuscular electrical stimulation (NMES) delivered at high intensities to the quadriceps muscle has been successful at improving quadriceps muscle strength and activation in patients who have undergone anterior cruciate ligament reconstruction and total knee arthroplasties.[14–16] However, the efficacy of NMES to improve quadriceps muscle function in people with early-stage OA is lacking.

In this study, we evaluated whether NMES was capable of improving quadriceps muscle strength and activation in people with mild to moderate OA. Our hypothesis was that participants who received the NMES intervention would demonstrate improvements in both quadriceps muscle strength and activation compared with participants who received no treatment.

Method

Participants

Participants were recruited from an OA registry at the University of Michigan. All volunteers in this registry have radiographic evidence of OA, defined as a score of ≥2 on the Kellgren and Lawrence (K-L) scale.[17] One hundred twenty-three women listed in the registry had a K-L scale score of 2 or 3 and were screened for eligibility via a telephone interview

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The Bottom Line

What do we already know about this topic?

Neuromuscular electrical stimulation (NMES) has been shown to be effective in improving quadriceps femoris muscle strength and activation in patients who have undergone knee replacement and ligament reconstruction. It is unknown whether NMES is capable of improving quadriceps function in a nonsurgical population, such as people with mild to moderate knee osteoarthritis.

What new information does this study offer?

Neuromuscular electrical stimulation, as delivered in this study, was incapable of improving quadriceps strength and activation. Increasing the dosage of the intervention, either by increasing the intensity of the stimulation or prolonging the length of delivery, may result in more favorable outcomes; however, further research is necessary to confirm or refute this premise.

If you're a patient, what might these findings mean for you?

Women with radiographic evidence of mild or moderate knee osteoarthritis are not likely to improve thigh muscle (quadriceps) strength with a short course of NMES.

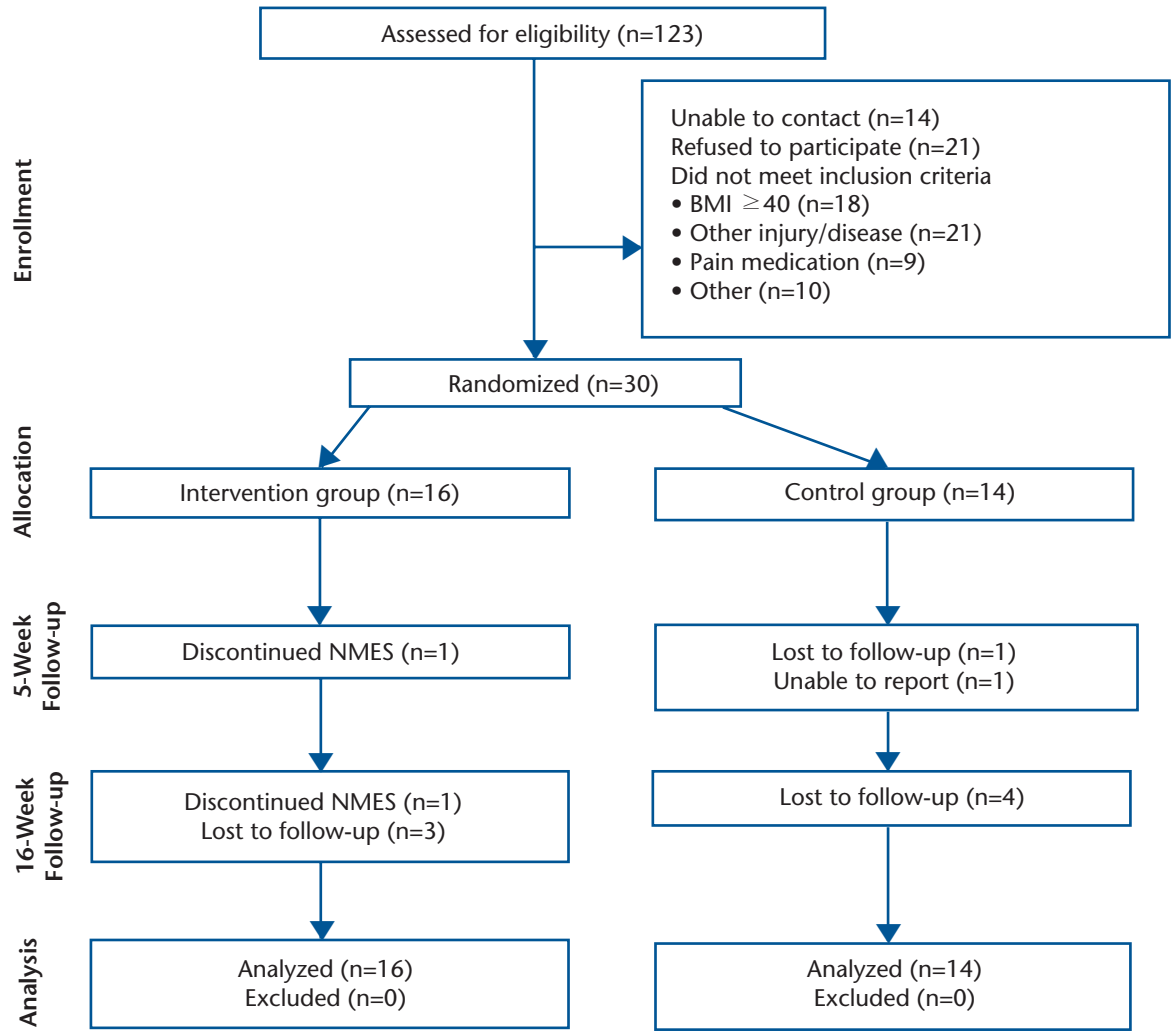

Figure 1.
Consolidated Standards of Reporting Trials diagram. BMI=body mass index, NMES=neuromuscular electrical stimulation.

(Fig. 1). Women were excluded if they: (1) had previously undergone a total knee arthroplasty or tibial osteotomy; (2) had diagnosed arthritis of the hip, ankle, or foot; (3) had a body mass index of ≥40; (4) used an assistive device while ambulating; (5) had a disease of the central or peripheral nervous system; (6) had any cardiac pathology; (7) reported a previous ligamentous knee injury; or (8) had previously undergone NMES therapy for OA. Women also were excluded if they were currently undergoing physical therapy for any lower-extremity orthopedic condition, taking COX-2 inhibitors, or receiving corticosteroid or hyaluronic acid injections. All participants provided written informed consent prior to enrollment.

Radiographic Evaluation

All women in the OA registry had anterior-posterior knee radiographs (model X-GE MPX-80*) within 12 months (mean=9.2 months) of study initiation. Bilateral, weight-bearing, semi-flexed radiographs were assessed for evidence of OA according to the K-L scale criteria, a standardized approach in which higher scores indicate greater disease severity, by one of the authors (M.F.S.) and a musculoskeletal radiologist.[17] Radiographs of knee joints where K-L scale score agreement was not achieved between the 2 readers were re-read and, if required, subjected to a consensus reading performed by a separate musculoskeletal radiologist. The inter-reader reliability between the study investigator and musculoskeletal radiologist was high (kappa=.92). The methods and procedures for reading and standardizing the radiographs are described elsewhere.[18]

* General Electric Co, 5730 N Glen Park Rd, Milwaukee, WI 53209-4403.

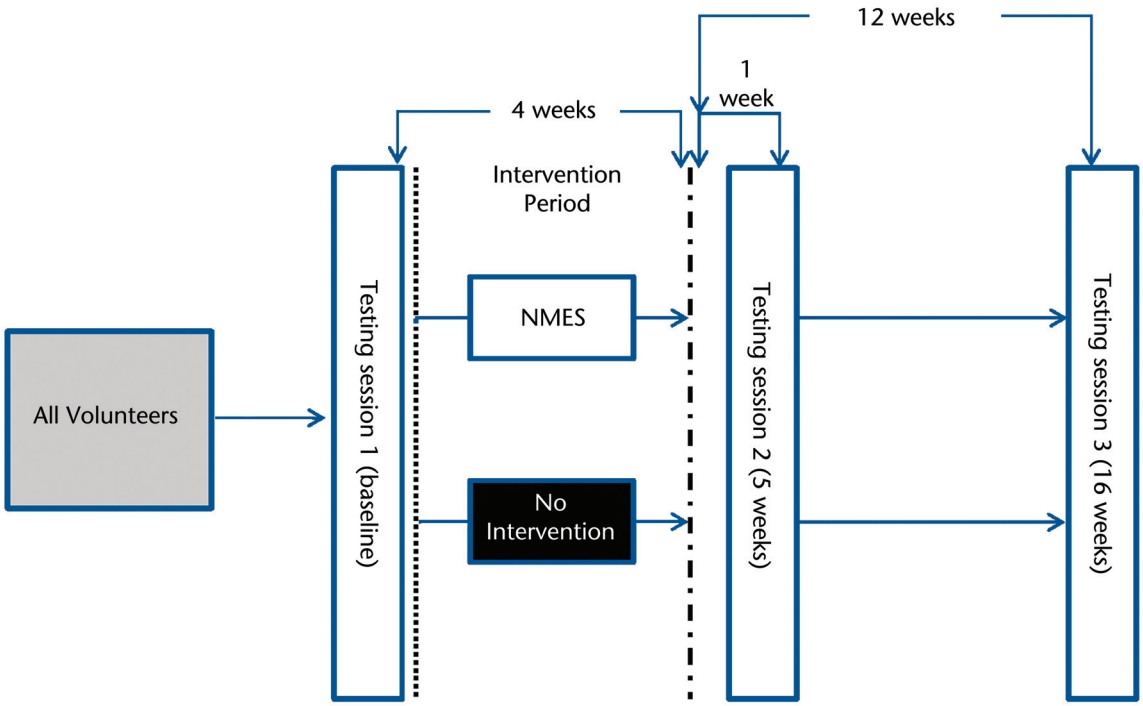

Figure 2.
Study testing timeline. All participants completed 3 testing sessions. Testing sessions took place at the time of study enrollment and at 5 and 16 weeks after study enrollment. The 5- and 16-week time points represent 1 week and 12 weeks after neuromuscular electrical stimulation (NMES), respectively, for the intervention group. Dotted line indicates randomization to group; dashed-dotted line indicates the end of the intervention period.

Each knee joint was classified as: 0=normal knee (no OA), 1=doubtful OA, 2=mild OA, 3=moderate OA, or 4=severe OA. Women eligible for inclusion had a K-L scale score of 2 or 3. Women with bilateral knee OA were included; however, these participants had to have a K-L scale score no greater than 3 in both knees.

Randomization and Intervention

Randomization and assignment were blind and conducted independently by one of the authors (R.P.S.) independently of intervention implementation and data analysis. Eligible participants were randomly assigned to 1 of 2 groups using a computer-generated random-number sequence from a randomization table and assigned into blocks of 4 participants. Allocation to groups included using sealed envelopes with slips of paper labeled with an I or C, signifying assignment to the intervention group or the control group, respectively. Envelopes were opened, and randomization occurred only after a participant met all inclusion criteria and successfully completed the baseline study evaluation.

Sixteen women were assigned to the intervention group, and 14 women were assigned to the control group. Women assigned to the intervention group received NMES 3 times per week over 4 weeks, for a total of 12 NMES treatment sessions. Women assigned to the control group received no intervention during the course of the study, as this is considered the standard of care for people not currently seeking physician involvement or treatment of any kind.

Each of the 12 NMES treatment sessions consisted of 10 electrically induced contractions of the quadriceps musculature. This course of intervention has been reported to improve quadriceps muscle strength.[10,15] The NMES was delivered to one limb only, either the osteoarthritic limb in cases of unilateral OA or the weaker limb identified during the baseline study evaluation in cases of bilateral OA. During each treatment session, each woman was seated in a chair with her leg positioned in 90 degrees of flexion and fixed to a pad that was attached to a load cell. Self-adhesive electrodes (2.75 × 5 in [6.98 × 12.7 cm], Dura Stick II[†]) were positioned proximally over the rectus femoris muscle and distally over the vastus medialis muscle. Quadriceps muscle contractions were elicited using a commercial electrical stimulating

[†] Chattanooga Group Inc, 4717 Adams Rd, Hixson, TX 37343.

unit (Vectra Genisys[†]) delivering a 2,500-Hz alternating current, modulated at 50 bursts per second, with a ramp-up time of 2 seconds.[16] The electrical current was set for a sequence of 10 seconds on (which includes the 2-second ramp-up time)[16] and 50 seconds off. Current intensity was set at each woman's maximum tolerance, although a target intensity of at least 35% of the participant's daily knee extension maximum voluntary isometric contraction (MVIC) was encouraged. Throughout the treatment sessions, the women were instructed to not contract their quadriceps muscles during the application of the stimulus. The same investigator delivered the intervention to all of the women assigned to receive NMES.

The percentage of the quadriceps muscle MVIC generated by the NMES intervention was determined during each treatment session for each participant to ascertain how closely the tolerated stimulus intensity chosen by each woman came to matching the target intensity set by the investigators (ie, a stimulus intensity that would produce 35% of their daily MVIC). After the baseline evaluation session, women in the control group did not receive any intervention, but were instructed to maintain their current activities throughout the course of the study. Participants in the intervention group were given similar instructions regarding the maintenance of activity.

Testing Procedures

Every participant, regardless of group assignment, was assessed at the time of study enrollment (baseline), as well as at 5 (primary time endpoint) and 16 weeks following study entry (Fig. 2). Follow-up time points were selected to assess both the immediate and sustained effects of the NMES therapy on the primary outcomes (quadriceps muscle strength and activation). Each of the 3 testing sessions included: (1) quadriceps muscle strength and activation assessment, (2) administration of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[19] and (3) a timed walk. Testing order was randomized for each participant prior to enrollment. All data collections took place between June 2008 and August 2009.

Data were collected in a single research laboratory by one of the authors (A.C.T.), a certified athletic trainer, who was trained to assess all outcome measures, but who was not blinded to group assignment. At the start of the trial, the assessor was able to conduct testing for quadriceps muscle strength, quadriceps muscle activation, and the timed walk reliably within and between sessions (intraclass correlation coefficient $\geq$.92).

Quadriceps Muscle Strength and Activation Assessment

Participants were positioned in an isokinetic dynamometer (System 3[‡]) with their hips flexed at 85 degrees, their knees flexed to 90 degrees, and their backs supported. The test limb was secured to the dynamometer arm, and a stabilization strap was secured over the pelvis. For women in the intervention group, the test limb was the limb subjected to the NMES intervention. The test limb for participants in the control group was either the osteoarthritic limb (in cases of unilateral OA) or the weaker limb established at the time of baseline testing when bilateral OA was present. Two self-adhesive electrodes of the same size as those used to deliver the NMES intervention were applied to the quadriceps muscle. Participants were asked to complete 3 submaximal isometric knee extension contractions to familiarize themselves with the testing procedures. Following the practice trials, 3 quadriceps muscle MVICs were performed, with 2 minutes of rest provided between contractions. When volunteers reached their peak torque during each of the MVIC trials, a supramaximal burst of electrical stimuli (100 pps, 600-μs pulse duration, 100-millisecond train duration, and 130 V) was delivered (Grass S88[§] and SIU8T[§]) in accordance with the burst superimposition technique.[20]

Torque data were exported in real time during the collections to a separate data acquisition unit (MP100[‖]). Quadriceps muscle activation was calculated using the central activation ratio (CAR), where the peak torque generated during the MVIC is divided by the peak torque generated from the electrical stimulation. A CAR of 1.00 represents complete quadriceps muscle activation. The trial with the largest quadriceps muscle MVIC torque was normalized to body mass (N·m/kg) and submitted to statistical analysis. The CAR calculated from the trial with the largest MVIC also was used in the data analysis.

Pain and Function Assessments

Women rated their knee pain, stiffness, and disability on a scale from 1 to 5 or none to extreme using the 5-point Likert version of the WOMAC.[19] Both the pain and disability components were scored to quantify patient-reported knee pain and function. Lower scores are associated with less pain and better functioning.

Participants also completed a timed 40-foot (12.19-m) walk,[21,22] which served as a quantitative measure of functional performance. Participants

[‡] Biodex Medical Systems Inc, 20 Ramsey Rd, Shirley, NY 11967-4704.

[§] Astro-Med Inc, 600 E Greenwich Ave, West Warwick, RI 02893.

[‖] Biopac Systems Inc, 42 Aero Camino, Goleta, CA 93117.

Table 1.
Baseline Demographic and Clinical Characteristics for the Intervention and Control Groups[a]

Variable	Intervention Group (n=16)	Control Group (n=14)	*P*
Age (y)	58 (2.7)	56.8 (2.9)	.25
Height (cm)	162.3 (7.4)	163.3 (4.5)	.61
Mass (kg)	86.3 (13.6)	87.8 (12.5)	.76
BMI	32.7 (4.1)	32.1 (5.1)	.76
Quadriceps muscle CAR	0.90 (0.08)	0.83 (0.15)	.10
Quadriceps muscle MVIC (N·m/kg)	1.24 (0.35)	1.29 (0.46)	.74
WOMAC pain subscale score (range=5–25)	7.6 (2.7)	8.9 (4.3)	.35
WOMAC disability subscale score (range=17–85)	27.1 (12.1)	28.8 (15.3)	.75
Timed walking speed (m/s)	1.43 (0.19)	1.40 (0.13)	.67
Kellgren and Lawrence scale score (% of grade 2)	93.8	92.9	1.00
Bilateral knee OA (%)	56	71	.47
Symptomatic OA (%)	50	50	1.00

[a] Values are means (SD) unless otherwise noted. No significant differences between groups were noted for characteristics at baseline. For the purpose of defining a woman as symptomatic or not symptomatic, we used the Likert scale included within the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). This scale asks participants to rate the level of pain in their knees during the 48 hours prior to testing. Women rating their knee pain as 2 or greater were considered to be symptomatic. BMI=body mass index, CAR=central activation ratio, MVIC=maximum voluntary isometric contraction, OA=osteoarthritis.

were instructed to walk down a tiled hallway at a purposeful (ie, brisk) pace. Participants completed 3 trials, and the trial with the fastest speed was used in the data analysis.

Data Analysis

An *a priori* power analysis indicated that 12 participants per group were needed to achieve 80% statistical power based on previous work examining the effects of NMES on quadriceps muscle strength and CAR after total knee arthroplasty.[16] Projected effect sizes (Cohen *d*) of 3.14 (strength) and 1.19 (CAR) were calculated using data that compared the CAR and MVIC prior to and 3 months following NMES in a treatment group.[16]

Therapeutic efficacy was assessed using an intent-to-treat analysis. The primary outcome measures for this study were the quadriceps muscle MVIC and CAR, and the secondary outcome measures were the WOMAC pain and disability subscales and the timed walk. To ensure that covariates were successfully randomized between the intervention and control groups, demographic and clinical characteristics were compared from the trial baseline assessment using chi-square tests, independent *t* tests, and Fisher exact tests, as appropriate.

Linear mixed modeling with repeated measures was used to assess whether there was a change in the dependent variables. The model specifications included 2 independent variables (ie, group and time), as well as a group × time interaction term, to assess whether there were different group effects at the 3 time points. Time was treated as a class variable, which allowed the comparison of week 5 versus baseline and week 16 versus baseline. An unstructured covariance matrix was selected for use in the mixed model, which allows for potential missing data assumed to be missing at random. Missing data were accounted for using case-wise deletion. The alpha level for all tests was set at $P \leq .05$. We used SAS version 9.2[#] for statistical analyses.

Change scores (follow-up − baseline) were calculated for both primary and secondary outcome measures. Effect sizes were quantified for each group between the baseline and follow-up time points using the Cohen *d* method (group mean baseline − group mean at follow-up divided by the pooled standard deviation).

Results

There were no statistically significant differences in baseline demographic or clinical characteristics (Tab. 1), suggesting successful randomization. Data for all 30 participants who were randomly assigned to a group, including those who either violated protocol or were lost to follow-up, were included in the analyses (Fig. 1).

Adverse Effects

No adverse events related to the NMES treatment were reported. One participant in the intervention group had reported having heart palpitations, which she attributed to the burst superimposition testing. The heart palpitations did not occur during any of the testing or treatment sessions, but rather occurred at home and did not begin on days in which the woman participated instudy-related activities. At the time the complaint was reported, the woman had finished re-

[#] SAS Institute Inc, PO Box 8000, Cary, NC 27513.

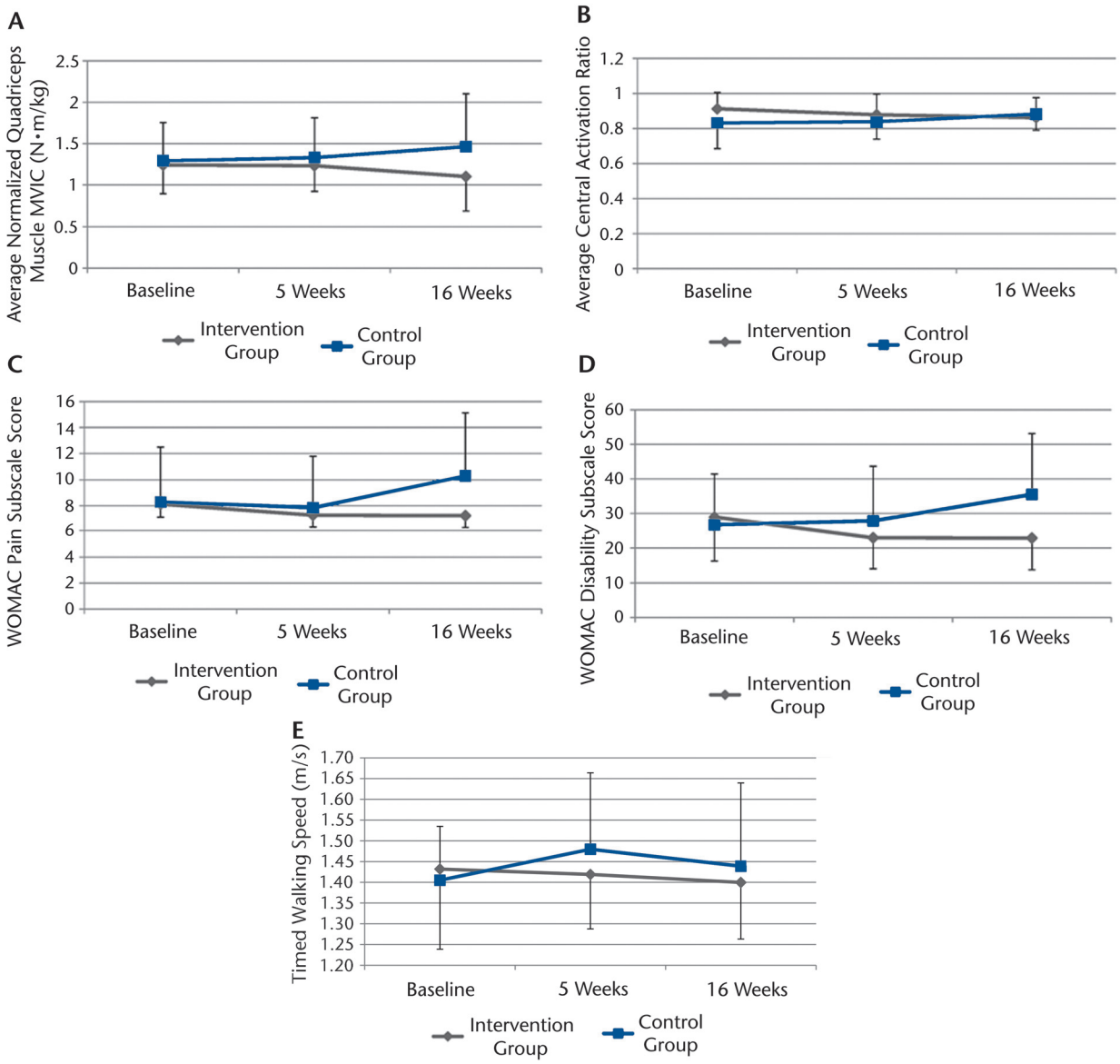

Figure 3.
A graphical representation of the means (SD) for all primary and secondary outcome measures over the 3 time points (baseline, 5 weeks, and 16 weeks) for both groups (intervention and control): (A) quadriceps muscle maximum voluntary isometric contraction (MVIC), (B) central activation ratio, (C) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score, (D) WOMAC disability subscale score, and (E) timed walking speed. No significant differences were noted between the groups at any of the 3 time points ($P>.05$).

ceiving the intervention. Her physician cleared her to participate in the remaining portions of the study (ie, the 5- and 16-week follow-up sessions), which she did but opted not to undergo the burst superimposition testing.

Protocol Adherence

Of the 16 women assigned to the intervention group, 14 completed all 12 treatment sessions, as per the treatment protocol. The women in the intervention group were able to tolerate a stimulus intensity to achieve the target MVIC percentage of 35% or greater in 93% of the treatment sessions.

Primary Outcome Measures: Quadriceps Muscle Strength and CAR

No significant main effects were identified for the intervention group

Table 2.
Mean Change Scores (95% Confidence Intervals) for the Primary and Secondary Outcome Measures at the 5- and 16-Week Follow-up Time Points[a]

Measure	Intervention Group (n=16)		Control Group (n=14)	
	5 Weeks	16 Weeks	5 Weeks	16 Weeks
CAR	−0.02 (−0.07 to 0.02)	−0.04 (−0.11 to 0.03)	0.01 (−0.09 to 0.10)	0.02 (−0.06 to 0.10)
MVIC	−0.03 (−0.21 to 0.14)	−0.21 (−0.50 to 0.08)	0.05 (−0.22 to 0.31)	0.14 (−0.20 to 0.49)
WOMAC pain subscale score	−0.53 (−2.37 to 1.30)	−0.54 (−1.83 to 0.75)	0.00 (−1.16 to 1.16)	1.4 (−0.26 to 3.06)
WOMAC disability subscale score	−4.86 (−11.29 to 1.56)	−4.92 (−10.89 to 1.05)	0.00 (−5.00 to 5.00)	5.0 (0.59 to 9.41)
Timed walking speed	−0.04 (−0.09 to 0.01)	−0.05 (−0.13 to 0.03)	0.00 (−0.02 to 0.20)	0.04 (−0.09 to 0.17)

[a] Negative values reflect a decrease from baseline; positive values reflect an increase from baseline. Baseline data were subtracted from follow-up data to calculate the scores. CAR=central activation ratio, MVIC=maximum voluntary isometric contraction, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

versus the control group (MVIC: $P=.74$; CAR: $P=.08$) or for week 5 (MVIC: $P=.60$; CAR: $P=.85$) or week 16 (MVIC: $P=.42$; CAR: $P=.23$) versus baseline for either of the primary outcomes. The group × time interaction terms in the modeling were not statistically significant, indicating that the intervention and control groups did not differ at week 5 or week 16 on either the MVIC ($P=.59$ and $P=.15$, respectively) or the CAR ($P=.43$ and $P=.09$, respectively) (Fig. 3). Table 2 presents the change scores and 95% confidence intervals for the primary outcome measures. Table 3 provides the within-group effect sizes and 95% confidence intervals for the primary outcome measures.

Secondary Outcome Measures: WOMAC and Timed Walk

No significant main effects were identified for the intervention group versus the control groups (WOMAC pain subscale: $P=.90$; WOMAC disability subscale: $P=.66$; timed walk: $P=.89$) or for week 5 versus baseline (WOMAC pain subscale: $P=.47$; WOMAC disability subscale: $P=.84$; timed walk: $P=.34$). However, when comparing week 16 versus baseline, the average WOMAC pain and WOMAC disability scores were significantly greater ($P=.05$ and $P=.03$, respectively), but there was no significant effect for timed walk ($P=.39$). The group × time interaction term for week 16 was significant for WOMAC pain and disability subscale scores, indicating that there were differences between the intervention and control groups at this time point ($P=.04$ and $P=.003$, respectively); with women assigned to the control group having greater WOMAC pain and disability subscale scores than those assigned to the intervention group. Neither of the group × time interaction terms were significant for the timed walk, indicating there were no differences in walking speed between the intervention and control groups at week 5 ($P=.73$) or week 16 ($P=.96$). Table 2 presents the change scores and 95% confidence intervals from baseline for the secondary outcome measures. Table 3 provides the within-group effect sizes and 95% confidence intervals for the secondary outcome measures.

Discussion

Quadriceps muscle weakness impairs functional ability and may be related to the onset of OA. Thus, identifying interventions capable of improving quadriceps muscle strength may improve quality of life in patients with this disease. This clinical trial of NMES was designed to evaluate the potential to improve quadriceps muscle strength and activation in a group

Table 3.
Within-Group Effect Sizes (95% Confidence Intervals) at the 5- and 16-Week Follow-up Points[a]

Measure	Intervention Group (n=16)		Control Group (n=14)	
	5 Weeks	16 Weeks	5 Weeks	16 Weeks
CAR	0.20 (−0.53 to 0.91)	0.42 (−0.36 to 1.18)	0.00 (−0.78 to 0.78)	−0.33 (−1.15 to 0.51)
MVIC	0.12 (−0.60 to 0.84)	0.46 (−0.33 to 1.21)	−0.06 (−0.85 to 0.72)	−0.29 (−1.11 to 0.55)
WOMAC pain subscale score	0.26 (−0.45 to 0.96)	0.30 (−0.44 to 1.03)	0.07 (−0.70 to 0.84)	−0.45 (−1.25 to 0.39)
WOMAC disability subscale score	0.55 (−0.18 to 1.25)	0.55 (−0.21 to 1.27)	−0.08 (−0.85 to 0.69)	−0.55 (−1.36 to 0.29)
Timed walking speed	0.06 (−0.67 to 0.79)	0.31 (−0.47 to 1.06)	−0.45 (−1.21 to 0.35)	−0.18 (−0.99 to 0.54)

[a] Effect sizes were computed using the Cohen *d* method (mean difference between baseline and follow-up/pooled standard deviation). CAR=central activation ratio, MVIC=maximum voluntary isometric contraction, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

of women with mild or moderate knee OA. Contrary to our hypothesis, the women who received NMES did not demonstrate significantly increased strength or activation following completion of the intervention protocol.

The current clinical trial used an NMES intervention protocol similar to those demonstrated to be effective in people following anterior cruciate ligament reconstruction[10,14,15,23] and total knee arthroplasty.[16] Protocols deemed efficacious do vary slightly, but most include a 2,500-Hz, alternating current, a current intensity eliciting at least 10% of the individual's MVIC, and a duration of 4 to 10 weeks. As the total duration of the intervention and the intensity at which it was delivered were similar to those of these other protocols, we believe the primary reason for the absence of an effect is related to the magnitude of quadriceps muscle strength and activation deficits demonstrated by our participants at the time of enrollment. Previously published data demonstrated that quadriceps muscle weakness was present in people with mild to moderate OA (K-L scale scores of 2 and 3), but that the magnitude of this weakness was not large, with apparent strength deficits equaling approximately 10% to 14% compared to adults who were healthy and of a similar age.[13,24] On the contrary, the magnitude of weakness evident initially after total knee arthroplasty can be at least 40% when compared with the unaffected limb,[25] and the weakness present initially after anterior cruciate ligament reconstruction can be upwards of 70% compared with the uninjured limb.[26] Similarly, the magnitude of activation failure can be upwards of 30% following total knee arthroplasy[27] and 25% after anterior cruciate ligament reconstruction.[28] As these magnitudes of strength and activation deficits are substantially larger than those found in the current study, it could be argued that effectiveness of NMES may be dependent on the magnitude of activation or strength deficits. Although there are no data to directly support this contention, in instances where NMES has been proven to be effective, the activation deficits demonstrated were markedly larger (Mintken et al[29]: CAR=0.729; Stevens et al[16]: CAR=0.594) compared with those found in the current study.

Another consideration relates to the magnitude of quadriceps muscle weakness and activation failure and the NMES dosage. In instances where quadriceps muscle strength and activation deficits are great, as is often the case following knee replacement and ligament reconstructive surgery, NMES may be effective at lower doses (eg, over shorter time periods and at lower intensities), whereas people with less weakness and activation failure may require greater doses to realize gains in quadriceps muscle strength and activation. This observation is supported by the work of Talbot et al,[30] who noted increased quadriceps muscle strength following 12 weeks of NMES (completed at home using a battery-operated stimulator, 3 times per week for 12 weeks, 15 contractions per session, with progressive increases in intensity every 4 weeks [weeks 1–4: 10%–20% of MVIC; weeks 5–8: 20%–30% of MVIC; and weeks 9–12: 30%–40% of MVIC]) in elderly people with symptomatic OA. Additionally, recent work suggests a dose-response relationship for NMES, with higher doses of NMES associated with less quadriceps muscle strength loss following total knee arthroplasty.[31] The ideal dose of NMES for people with mild to moderate OA is unknown and warrants further study; however, it is apparent that 4 weeks of NMES at intensities sufficient to generate at least 35% of the MVIC are inadequate in this population.

Quadriceps muscle weakness related to OA may stem from voluntary activation failure (ie, an inability to fully activate the quadriceps muscle) or muscle atrophy.[27,32,33] Neuromuscular electrical stimulation is thought to improve activation and induce hypertrophy, resulting in gains in strength.[16,29,34–36] However, based on its duration and intensity, our NMES protocol would be more likely to improve activation rather than induce muscle hypertrophy (reducing activation deficits may be more critical than reducing atrophy, as physical function is more severely affected in patients with OA who have greater activation deficits[4]).

Muscle hypertrophy is typically thought not to be discernible until 8 to 12 weeks after initiating resistance training,[37–40] although some research suggests hypertrophy can occur earlier.[41] Therefore, strength gains achieved before 8 weeks generally are thought to result from neural improvements, such as a decline in activation failure.[37–40] Furthermore, research completed in elderly people who were healthy suggests training intensities upward of 50% to 60% of the MVIC are needed to induce hypertrophy.[42]

When considering these findings, our NMES protocol probably did not alter the structural characteristics of the muscle. This distinction is important because we are aware of no data that highlight the contributions of both activation failure and atrophy to quadriceps muscle strength in people with early to moderate OA. If atrophy is the primary contributor to quadriceps muscle weakness, then the intervention, as delivered, may be unlikely to improve muscle strength, and this fact could have contributed to our null results. However, if activation failure predominantly causes the muscle weakness, then we would have expected to see some benefit from the intervention,

if the NMES intensity was sufficient for women with mild to moderate OA. As the women participating in this trial had an average CAR of 0.873 (coefficient of variation=7%) and elderly people who were healthy displayed an average activation ratio of 0.955,[43] we would surmise that voluntary activation failure was likely present in many of women in our study groups and at least partially contributed to the existing quadriceps muscle weakness. Therefore, we again suggest that the dosage provided was not of a sufficient intensity to improve muscle strength or activation in our study population. Future research should focus on examining the dose-response relationship in people at various stages of the OA disease process.

If the dosage of NMES is critical in improving quadriceps muscle strength and activation in people with early OA, altering the protocol for future studies is reasonable. Such protocol changes may include increasing the quantity and duration of NMES treatments; however, increasing the intensity of the stimulation may not be realistic. To achieve quadriceps muscle contractions of a sufficient intensity for the current trial, some participants were quite uncomfortable. Furthermore, in some instances, the stimulus was delivered near the maximum allowable by the electrical stimulation unit. Therefore, in instances where minimal to moderate muscle weakness is present and where higher dosages of NMES treatment may be warranted, increasing the duration of the intervention may be necessary, but future studies are needed to evaluate this. An additional consideration meriting discussion is using NMES along with quadriceps muscle resistance exercises, which yielded favorable results in a study by Petterson et al.[11]

The intervention for our study was delivered to a group of women with radiographic evidence of OA who reported mild symptoms and minimal disability. It is possible, therefore, that the use of NMES in women with few symptoms may not be effective despite the dosage utilized. Intervening in people with minimal or no symptoms and radiographic evidence of OA appeared justified given available data suggesting that quadriceps muscle strength in women may be involved in incident symptomatic OA.[13]

Although NMES appeared to have little effect on quadriceps muscle strength and activation, it did appear to influence WOMAC scores. Women in the intervention group displayed lower WOMAC pain and disability subscale scores compared with women in the control group at the 16-week time point, suggesting less pain and greater function in the women who underwent NMES therapy. When examining the data closely (see Fig. 3, graphs C and D), it becomes apparent that pain and function worsened by week 16 in the control group, whereas women in the intervention group had similar (pain) or improved (function) scores at week 16. This finding may suggest that NMES could be effective at delaying or preventing the progression or onset of OA symptoms. As neither group displayed changes in quadriceps muscle strength or activation during the study period, the symptom-preventing effect that the intervention group displayed is likely not the result of improved quadriceps muscle function, nor is the worsening of OA symptoms in the control group likely related to decrements in quadriceps muscle function. The reasons why self-reported pain and function were worse in the control group compared with the intervention group at week 16 are unknown and warrant further study.

Although statistically significant differences between groups at 5 weeks were not apparent for the WOMAC disability subscale score, it should be pointed out that a moderate effect (Cohen $d=0.55$) was noted between baseline and the 5-week follow-up for the intervention group. Women undergoing NMES therapy did seem to realize clinically relevant improvements in physical functioning, as defined by the WOMAC, after receiving treatment. These clinically meaningful self-reported improvements also may have manifested during the timed walk, although the effect size for this variable was small. At week 5, the women in the control group slowed their walking speed by ~0.08 m/s, which in older adults is considered to be a meaningful change in physical function.[44,45] Whether this rather small decline in speed is clinically meaningful in people with OA remains unknown and should be examined.

This study is not without limitations. First, the women in our clinical trial were enrolled based on radiographic evidence of OA and did not necessarily report symptoms of the disease. Only half of the present study sample reported symptoms. People with radiographic OA and without symptoms may not respond to NMES therapy, and this fact could have contributed to our null finding. Future studies should consider examining the effects of NMES on individuals who are symptomatic and asymptomatic separately, especially considering that people with symptomatic OA may have fewer pain-free exercise alternatives, and thus it is important to ascertain its efficacy in this population. Second, though we conducted an *a priori* power evaluation to determine the number of participants to enroll in the trial, these calculations were completed using data where NMES had a large effect (ie, the values were taken before and after NMES therapy in people following total knee arthroplasty[16]). Therefore, the study may suffer from a type II statistical error, as the effect of NMES on people with mild to moderate OA is not as strong. Third, we did not blind the assessor

or the patients to group assignment, which may have introduced bias into the study. Finally, participants were tested and treated in the same positions, which may have affected our strength and activation outcomes. Given that no effect was demonstrated for the treatment, this concern is almost negated.

Conclusions

In this clinical trial, women with radiographic evidence of mild or moderate knee OA who were randomly assigned to receive an NMES intervention did not realize gains in quadriceps muscle strength or activation compared with the untreated group. The inability of NMES to improve quadriceps muscle function may be the result of the low magnitude of quadriceps muscle dysfunction present in the women in our study or the dosage of the intervention. The dose-response relationship for NMES should be determined in people with evidence of mild to moderate OA.

Dr Palmieri-Smith and Dr Sowers provided concept/idea/research design and writing. Dr Palmieri-Smith, Ms Thomas, and Ms Karvonen-Gutierrez provided data collection. Dr Palmieri-Smith, Ms Karvonen-Gutierrez, and Dr Sowers provided data analysis. Dr Palmieri-Smith provided project management, fund procurement, and facilities/equipment. Ms Thomas and Ms Karvonen-Gutierrez provided consultation (including review of manuscript before submission).

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