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Neuromuscular electrical stimulation after total joint arthroplasty: a critical review of recent controlled studies

A. J. KITTELSON [1], S. K. STACKHOUSE [2], J. E. STEVENS-LAPSLEY [1]

[1]*Physical Therapy Program*
Department of Physical Medicine and Rehabilitation
University of Colorado, Aurora, CO, USA
[2]*Department of Physical Therapy*
Arcadia University, Glenside, PA, USA

Since 2009, four randomized controlled trials have investigated the use of Neuromuscular Electrical Stimulation (NMES) as a treatment modality following total knee arthroplasty (TKA). Two of these studies demonstrated a treatment effect of NMES for improving physical function, while another study failed to find additional benefit of NMES relative to a progressive exercise intervention. The fourth study demonstrated non-inferiority of NMES compared supervised physical therapy. These studies differed substantially in their methodology, including the timing, duration, treatment volume and intensity of NMES interventions. The purpose of this review is to examine and discuss variations between these recent trials to synthesize the current state of evidence for NMES in post-TKA rehabilitation. When comparing intervention parameters across recent studies, it appears that high intensity NMES performed regularly during the immediate postoperative phase helped to attenuate dramatic losses in quadriceps strength following TKA, thereby resulting in overall improvements in strength and function.

Key words: Arthroplasty, replacement, knee - Quadriceps muscle - Electric stimulation.

Neuromuscular electrical stimulation (NMES) is often used as a quadriceps strengthening modality following total knee arthroplasty (TKA) surgery, to provide an adequate training dose to patients lacking sufficient volitional quadriceps activation, to engage neurophysiological mechanisms thought to facilitate strength gains, and to provide a general physical stress to the quadriceps neuromuscular system. The goal is to attenuate the dramatic strength loss that characterizes the immediate postoperative period following TKA and from which some patients fail to recover. Recently, NMES has received research attention in the form of several clinical studies, randomized controlled trials and a Cochrane review. These reports provide conflicting evidence for the overall effectiveness of NMES for improving quadriceps strength and physical performance in patients following TKA. However, the intervention parameters - including NMES settings, method of application, overall intensity and duration, and postoperative timing - differ substantially between studies. Thus, the purpose of this review is to critically appraise recent clinical trials in the context of physiological mechanisms for NMES, over the time course of quadriceps recovery following TKA.

Corresponding author: J. Stevens-Lapsley, MPT, PhD,UCD Physical Therapy Program, Mail Stop C244,13121 East 17th Avenue, Room 3116,Aurora, CO 80045.
E-mail: Jennifer.Stevens-Lapsley@ucdenver.edu

Strength and functional deficits following TKA

TKA is one of the most commonly performed surgeries, with approximately 1.3 million procedures performed annually in North America and Europe.[1] In the United States, over 650,000 TKAs are performed every year, making the procedure more common than elective coronary artery bypass graft, cholecystectomy, colorectal resection, spinal fusion, or hysterectomy.[2] In many countries, rates of TKA are growing at more than 10 percent per year, and the overall health and economic burden of TKA is expected to increase substantially in the coming decades.[1, 3] Although pain and self-reported function improve dramatically for many patients who undergo TKA,[4-6] objective physical performance deficits are often persistent, with patients demonstrating 63% slower timed up and go (TUG) times and 104% slower stair climbing speeds at 6 months after TKA, compared to healthy older adults.[7]

TKA is characterized by an immediate and dramatic loss of quadriceps strength that occurs as a result of surgery. Evidence suggests that quadriceps strength drops by 50-60% one month following surgery and fails to recover past preoperative levels for many patients.[7, 8] Relative to healthy older adults, quadriceps strength deficits have been shown to persist even 6-13 years following surgery.[9] Impairments in quadriceps strength have been associated with decreased walking speed, impaired balance, diminished sit-to-stand ability, and an increased risk for falls, suggesting that quadriceps weakness may directly impact important indicators of overall physical health and independent living.[8, 10-16]

The etiology of quadriceps weakness following TKA is multifactorial and may be attributed to the trauma of surgery as well as to pre-existing factors associated with the pathology of osteoarthritis (OA) and comorbidites (such as obesity and poor cardiovascular health) that are often present in patients with knee OA. Broadly speaking, the mechanisms behind quadriceps weakness might be conceptualized as 1) mostly muscular in nature (stemming from factors such as decreased muscle mass); or 2) mostly neural in nature (including factors such as impaired voluntary activation).[17] Both of these mechanistic categories are known to contribute to quadriceps weakness in patients with knee OA,[17] as well as following TKA surgery.[8, 18] However, neural contributions to muscle weakness are thought to predominate in the early postoperative period following TKA, likely giving way to factors such as disuse atrophy later in the recovery process (Figure 1).[8] In fact, these early neural contributions to quadriceps weakness may further exacerbate long-term weakness by contributing to low physical stress and general disuse of the surgical limb for the first weeks and months following surgery. Therefore, rehabilitation strategies that seek to target neural contributions to quadriceps weakness have the potential to maximize strength improvements in all phases of recovery, with the ultimate goal of restoring patients to the functional capacity of their healthy peers.

Neural mechanisms for quadriceps weakness following TKA

Immediately following TKA surgery, patients often exhibit a sharply diminished ability to activate the quadriceps muscle. Clinically, this can be manifested as poor performance of a straight leg raise or knee extension exercise. Patients may experience instability or buckling of the surgical knee during functional tasks, such as transfers or ambulation, or they may report intense mental exertion with even minimal efforts to contract the involved quadriceps. These difficulties often seem to occur independent of the intensity of post-surgical knee pain.[8] Experimentally, quadriceps activation deficits can be examined by superimposing a percutaneous electrical stimulus on a maximal voluntary isometric contraction (MVIC). It is beyond the scope of this paper to review all the specific research techniques used to assess quadriceps activation, but in general, the increased force output that occurs when an electrical stimulus is superimposed onto an MVIC can be used to quantify deficits in voluntary activation.[19-22]

The neurophysiologic mechanisms underlying activation deficits following TKA are not fully understood, although a confluence of pre-surgical, surgical and post-operative factors may be involved. Surgical damage to the knee joint is known to result in altered afferent feedback, which could lead to reduced quadriceps alpha motoneuron excitability in the spinal cord and diminished volitional force output. The presence of postoperative edema may influence gating mechanisms within the central nervous system at multiple locations, in turn reducing excitatory input to the muscles surrounding the affected joint.[23] The presence of edema may also affect the neural regulation of muscle tone, perhaps via Ruffini ending influences on the Golgi tendon organ.[24] Motor cortical mechanisms have been hypothesized to impact quadriceps activation deficits following TKA but have yet to be characterized, and the influence of pain on

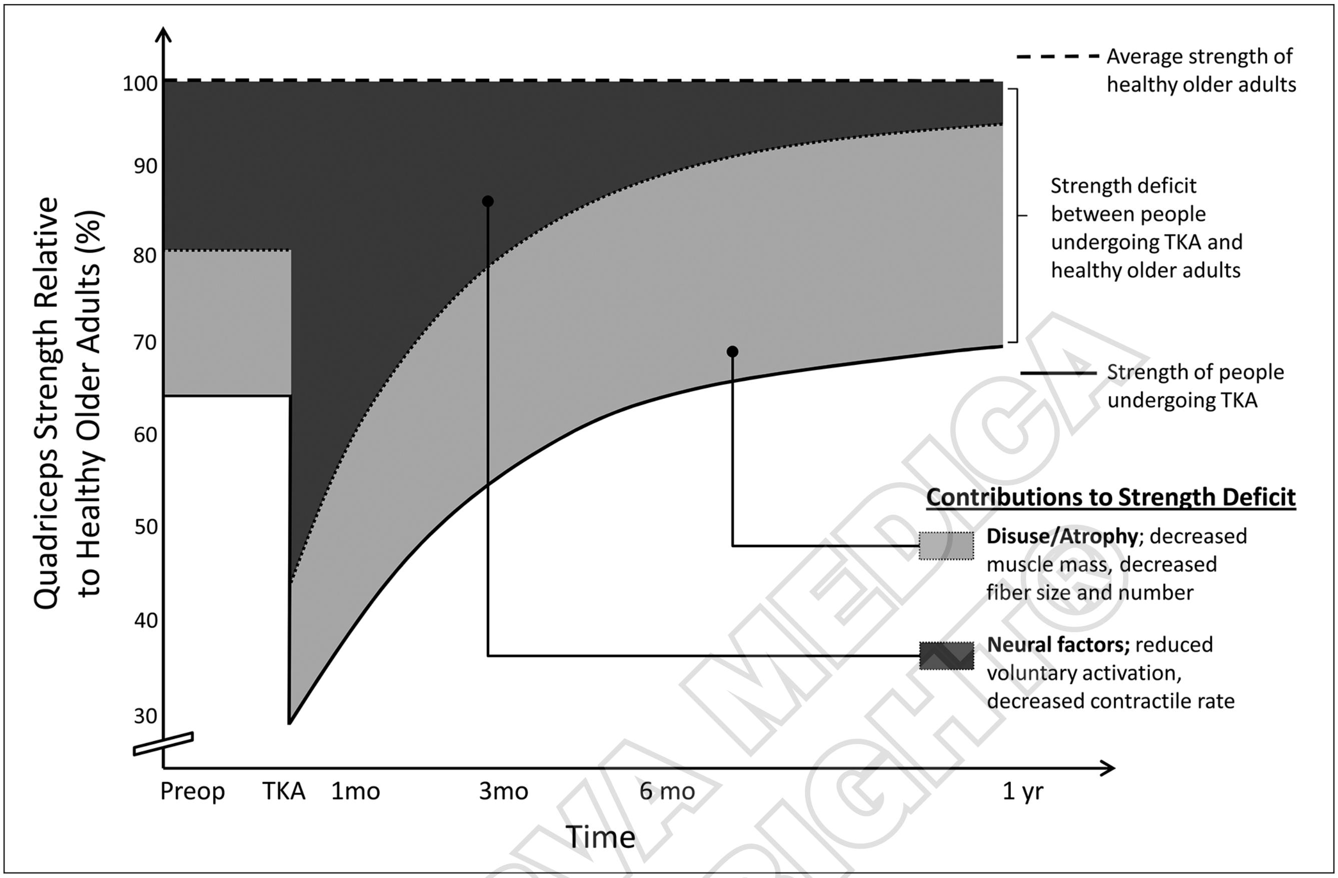

Figure 1.—A conceptual diagram of quadriceps strength before and after total knee arthroplasty (TKA), relative to healthy older adults. Deficits in strength are approximated based on recent longitudinal studies [7-9]. Neural contributions to quadriceps weakness are thought to predominate in the early postoperative period, leading to increased disuse of the surgical limb and associated with muscle atrophy later in the recovery process.

activation deficits has been studied in a variety of healthy and patient populations.[23, 25-26]

In patients with end-stage knee OA, the involved quadriceps has been shown to exhibit activation deficits of approximately 20% relative to the uninvolved limb, suggesting that neural mechanisms contribute to quadriceps weakness even prior to TKA surgery.[8, 17-18, 26, 27] One month following TKA, there is a further reduction in quadriceps activation of approximately 17%,[8, 28] although this is extremely variable, with some patients exhibiting much more pronounced activation deficits early after surgery. Thus, a strengthening protocol that calls for training at 75% of a one-repetition maximum following TKA surgery is likely to deliver a much smaller physiological load to the exercising muscle-perhaps less than 50% of the muscle's true force generating capability. Such dosages may not provide the overload required to induce real strength gains.[29] Therefore, strengthening methods that bypass or supplement voluntary muscle activation may be more effective for individuals in the early postoperative period following TKA.

NMES for the treatment of quadriceps weakness following TKA

NMES is sometimes employed as a strengthening modality in patient populations where voluntary activation is known to be compromised,[30-35] with the rationale that the intensity of the muscle contraction produced during electrical stimulation may provide a more adequate training dose than the intensity produced through voluntary contraction in the presence of marked activation deficits. NMES is also thought to alter motor recruitment by preferentially activating a greater proportion of larger, type II muscle fibers than through volitional exercise at comparable intensities.[36, 37] Furthermore, afferent input from NMES may facilitate plastic changes throughout sensorimotor networks in the central nervous system, ultimately enhancing strength and motor control.[38-42] These neural changes have been specifically sought for patients following neurologic injury. For example, in patients following stroke, a 77% improvement in quadriceps force and nearly 20% improvement in motor unit recruitment were achieved through NMES treatment, compared to minimal changes in a group of patients not receiving NMES.[43] Similar results have been shown for patients with cerebral palsy, with significant increases in strength, voluntary activation, quadriceps cross-sectional area, and walking speed observed in patients receiving NMES.[42]

Over the last several years, NMES has garnered a growing enthusiasm for the treatment of quadriceps weakness following TKA. Several case reports have documented improvements in strength and activation with the use of NMES for patients in both the early and long-term postoperative period.[44-47] A small-scale preliminary study suggested that the preoperative use of NMES may lead to greater strength gains in the first 3 months after TKA,[48] and Gotlin *et al.*. noted that NMES applied during the hospital stay (within the first week after TKA) reduced knee extensor lag relative to a control group.[49] Until recently, randomized controlled trials of NMES in patients undergoing TKA included small sample sizes and were thus not always powered to detect improvements in quadriceps strength.[50, 51]

Clinical trials of NMES in patients undergoing TKA

Since 2009, four randomized controlled trials have been have been published that examine the effects of NMES on postoperative strength and function for patients undergoing TKA.[27, 52-54] These studies vary in terms of sample size and patient population, how and when NMES was applied, and the outcomes and methods used to assess strength and functional recovery (Table I).[52-58] The results of the trials are mixed, with two studies reporting NMES is effective for improving physical performance,[27, 52] one study reporting that NMES fails to improve performance more than progressive resistance exercise alone,[54] and one study (designed as a non-inferiority trial) reporting that the isolated use of NMES is as effective as traditional physical therapy following TKA.[53] Potential sources of variability and differences between the trials are further summarized in the following sections.

TABLE I.—*A summary of recent clinical trials investigating NMES after TKA, including intervention parameters and results.*

Study	N. per group (NMES, control)	NMES intervention start-time	Duration/frequency of NMES intervention	NMES Intensity	Duty cycle (%)	NMES frequency (Pulses per second)	Pulse duration (µs)
Petterson *et al.*, 2009 [54]	100, 100	4 weeks after TKA	10 contractions, 2-3x/week for 6 weeks (12 visit target)	Max tolerance	11	50	~400*
Avramidis *et al.*, 2011 [52]	35, 35	Post-op day 2	2 hours, BID, extending for 6 weeks	Max tolerance	50	40	300
Stevens-Lapsley *et al.*, 2012 [58]	35, 31	Post-op day 2	15 contractions, BID, extending for 6 weeks	Max tolerance	25	50	250
Levin *et al.*, 2013	35, 35	14 days prior to surgery	NMES reinitiated the first postoperative day for 20-30 minutes per day, continued for 6 weeks	Max Tolerance	29	75	300

*calculated from reported carrier frequency of 2500 Hz [54]
BID = Twice per day; KOS-ADLS = Knee Outcome Survey, Activities of Daily Living Subscale; SF-37 = Short Form 36; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; GRS = Global Rating Scale; KSS = Knee Society Score; SCT = Stair Climbing Test; TUG = Timed Up and Go; 6MWT = 6 Minute Walk Test; 3MWT = 3 Minute Walk Test; HR = Heart Rate; AROM = Active Range of Motion.

Patient selection and demographics

In three of the four clinical trials, patient selection was carefully controlled to include relatively healthy people with unilateral knee osteoarthritis, so as to minimize the potential for confounding variables to influence the results. In these studies, patients were excluded if they reported significant pain in another lower extremity joint or if they had certain comorbidities that could impact postoperative recovery, such as uncontrolled diabetes or cardiovascular disease.[27, 52, 54] The exception was the study by Levine *et al.*, which did not exclude patients with bilateral OA or comorbid pain problems but did exclude patients with health issues such as lower-limb ischemia, epilepsy, or diminished cognitive function.[53] In the study by Petterson *et al.*, the patient population was primarily male (>50%),[54] whereas the sex distribution reported in other studies ranged from 52% female [27] to 83% female.[52] The average age of the participants in the study by Avramidis *et al.* was approximately 71 year old,[52] whereas the average age of the study populations in the other trials were slightly younger (approximately 65 year old). The participants in the study by Avramidis *et al.*. also had lower Body Mass Index (BMI) on average, compared to the other studies (approximately 27 kg/m² versus approximately 30 kg/m² in most other study groups). The largest trial was conducted by Petterson *et al.*, with 100 participants receiving a progressive resistance exercise intervention and 100 participants receiving NMES in combination with this exercise intervention. All other trials had group sizes ranging between 31 and 35 participants.

NMES parameters and intervention design

In general, NMES settings in all studies were consistent with an overall goal of muscle strengthening, although there was variation in the specific parameters used (Table I). Stimulation frequencies in all studies were sufficient to induce a tetanic muscle contraction, ranging from 40 pulses per second (pps) [52] to 75 pps.[53] Pulse durations ranged from 250 [27] to approximately 400 microseconds.[54] The duty cycle varied considerably between studies, as Avramidis *et al.* adopted a 50% cycle (8 seconds on, 8 seconds off), Levine *et al.*. adopted a 29% cycle (4 seconds on, 10 seconds off), Stevens-Lapsley *et al.* adopted a 25% cycle (15 seconds on, 45 seconds off) and Petterson *et al.* adopted an 11% cycle (10 seconds on, 80 seconds off). Each of the trials reported that NMES intensity was dosed according to maximal patient tolerance. Petterson *et al.* assessed the intensity of NMES by measuring the torque produced during NMES application, with a goal of achieving 30% of preoperative quadriceps MVIC torque. However,

Pad size (cm)	Self-report outcomes	Physical performance measures	Study results
7.62 X 12.70	KOS-ADLS, SF-36	Quadriceps Strength and Activation, SCT, TUG, 6MWT	No differences observed between NMES and control groups
7.0 X 7.0	SF-36, Oxford 12-item knee score	3MWT, physiological cost (HR change/walking speed)	NMES resulted in significantly better 3MWT, Oxford knee score and SF-36 at 6 weeks. SF-36 results persisted through 1 year.
7.62 X 12.70	WOMAC, SF-36, GRS	Quadriceps Strength and Activation, Hamstring Strength, SCT, 6MWT, TUG, AROM	NMES resulted in significant improvements in quadriceps and hamstring strength, SCT, 6MWT, TUG, and extension AROM at 3.5 weeks following TKA Results persisted through 1 year.
5.08 X 10.16	KSS, WOMAC	TUG, AROM	Non-inferiority of NMES (compared to supervised physical therapy) was demonstrated for all measures at 6 months following TKA

the proportion of patients that achieved the intensity goal of 30% was not reported. The study by Stevens-Lapsley *et al.* was the only trial to report the torque achieved during NMES, which ranged from 1.6% to 76.7% of preoperative MVIC (mean = approximately 17% MVIC).

In most cases, a rehabilitation protocol that involved some combination of strengthening, flexibility exercises, and training in functional activities was used as a control intervention, and NMES was applied as an adjunct to these exercises. Avrimidis *et al.* described the control intervention as "conventional physiotherapy," which commenced immediately following surgery and incorporated strengthening and stretching exercises beginning on the third postoperative day.[52] Petterson *et al.* and Stevens-Lapsley *et al.* described a control intervention that involved progressive strength training, dosed according to each patient's 10-repetition maximum, with a goal of performing 3 sets of 10 repetitions of each exercise. Major muscle groups of the lower extremity (including the quadriceps) were targeted in both weight bearing and non weight bearing positions.[27, 54]

In the study by Levine *et al.*, patients not receiving NMES were provided with 5 packets of exercises, including range-of-motion as well as progressive strengthening exercises. These exercises were performed under direct supervision of a physical therapist. Patients receiving NMES were instructed in home use of NMES and provided with additional descriptions of range-of-motion exercises (but not strengthening exercises), and rehabilitation was performed without direct supervision. The analysis investigated non-inferiority of the NMES intervention based on an arbitrarily defined 10% allowable difference between groups in the outcomes assessed.[53]

Timing, frequency, and duration of the intervention

The post-operative timing of NMES interventions, frequency of application and duration of treatment also varied considerably between studies (Table I). Levine *et al.* commenced NMES treatments two weeks prior to surgery, for 20-30 minutes daily. Treatments were not performed on the day of surgery but were resumed on the first postoperative day and continued for 6 weeks following surgery. Petterson *et al.* did not initiate NMES treatments until the fourth postoperative week, and at that point, treatments were performed at a frequency of two to three times per week, for the next six weeks. Each treatment consisted of 10 NMES cycles (10 seconds on, 80 seconds off). In the two remaining studies, treatments were initiated on the second postoperative day and performed twice daily for 6 weeks. However, in the study by Avrimidis *et al.*, NMES was performed for 2 hours at each treatment (four hours per day), whereas Stevens-Lapsley *et al.* performed 15 cycles (15 seconds on, 45 seconds off) at each treatment, for a total of 30 minutes daily. Thus, it appears that patients receiving NMES in the trial by Avrimidis *et al.* received NMES for the most cumulative time following surgery, whereas patients receiving NMES in the trial by Petterson *et al.* utilized NMES for the least amount of overall time. Levine *et al.* were the only group to initiate NMES prior to surgery.

Outcomes and study results

A variety of self-report and performance-based measures were used to investigate the effectiveness of NMES for improving outcomes following TKA (Table I). Quality of life was assessed using the 36-item Short Form Health Questionnaire in all studies except for the trial by Levine *et al.*, which did not assess global health status. Each of the studies included a self-report measure of knee function, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Outcome Score (KOS-ADLS), Global Rating Scale (GRS), or Oxford Knee Score (OKS). Levine *et al.* used also the Knee Society Score, which includes pain reports and orthopedic knee measures such as the degree of flexion contracture. Performance-based tests varied across trials but included functional tests such as the TUG, 6-minute walk test (6MWT), and 3-minute walk test (3MWT), as well as knee specific measures such as quadriceps strength, hamstring strength, and range of motion. Stevens-Lapsley *et al.* and Petterson *et al.* incorporated measures of quadriceps activation, and these two studies were also the only studies to include higher-demand functional assessments such as the stair climbing test (SCT) and 6MWT, which have been shown to demonstrate strong relationships with quadriceps strength after surgery and thus may act as functional surrogates of quadriceps performance.[16, 55]

In the trial by Stevens-Lapsley *et al.*, a robust treatment effect was observed. Patients receiving NMES demonstrated dramatically reduced strength and performance deficits early after surgery compared to those receiving only physical therapy. Furthermore, group differences persisted for the duration of the study - throughout the first postoperative year - such that patients receiving NMES achieved significantly larger overall improvements in quadriceps strength, hamstring strength, TUG and stair climbing time, and 6MWT distance. By six months following surgery, patients receiving NMES demonstrated 20% improvements in quadriceps strength relative to preoperative values (from 1.33 Nm/kg to 1.51 Nm/Kg), whereas patients in the control group hovered around their pre-surgical strength (1.32 Nm/kg preoperatively; 1.39 Nm/kg at 6 months). By one year following surgery, patients in the NMES group improved their 6MWT distance by an average of 120 meters, compared to pre-surgical levels, whereas patients in the control group improved by an average of 43 meters, which fails to meet the threshold for minimal detectable change and thus may not amount to a clinically meaningful improvement.[56]

Treatment effects were less dramatic in other studies. Avramidis *et al.* showed improvements in walking speed (as measured by the 3MWT) in the NMES group relative to the control group at 6 weeks and 3 months but not at one year. Self-report measures of function and quality of life were also significantly better in the NMES group over the first 3 months (group differences in self-report measures were generally not observed in the study by Stevens-Lapsley *et al.*). Strength was not assessed in the study by Avramidis *et al.*, so direct comparisons to the study by Stevens-Lapsley *et al.* cannot be made. Petterson *et al.* failed to find group differences in any of the outcomes assessed (strength, quadriceps activation, performance-based tests or self-report questionnaires) between patients receiving a progressive resistance exercise intervention and patients receiving progressive resistance exercise and NMES combined, but both arms of the clinical trial achieved better functional outcomes than a cohort of patients who did not enroll in the study and underwent standard of care physical therapy.[54] As mentioned, the study by Levine *et al.* was designed to examine non-inferiority of unsupervised NMES relative to supervised physical therapy following TKA, so the effects of NMES in addition to standard physical therapy cannot be assessed. Non-inferiority was demonstrated for all measures of performance (TUG, range of motion) and self-report (WOMAC) by 6 months following surgery.[53]

Discussion

A recent review of the effectiveness of NMES for quadriceps strengthening for patients undergoing TKA was conducted by the Cochrane Collaboration.[57] Two studies were included in this review: 1) Oldham *et al.*;[51] and 2) Stevens *et al.*,[58] a 2002 pilot study that provided preliminary data for the trial performed by Petterson *et al.* in 2009. The Cochrane review concluded that insufficient data existed on which to base recommendations for or against the use of NMES for quadriceps strengthening in patients undergoing TKA.[57] Both of the studies included in the review were criticized for their high risk of bias because of inadequate descriptions of certain parameters such as randomization and blinding. Furthermore, the trial by Oldham *et al.* included only patients with end-stage knee OA and did not follow patients after TKA.

Since the publication of this Cochrane review, four additional clinical trials have been conducted.[27, 52-54] These studies continue to suffer from methodological issues relating to risk of bias and overall quality. For example, blinding of assessors was not always possible due to the availability of study personnel,[27] and sociodemographic variables such as age, sex and BMI were not consistently reported, so the adequacy of randomization could not always be determined.[53] Furthermore, most of the studies excluded patients with significant health comorbidities or contralateral lower extremity pain.[27, 52, 54] Thus, the results of these studies are only generalizable to clinical populations with similar characteristics and the therapeutic validity of the broad application of these interventions might be brought into question.[59]

Two of the recent studies did not assess quadriceps strength or activation,[52, 53] which are thought to be two of the major physiological targets of NMES as an intervention. Therefore, in these studies, it is difficult to infer the physiological mechanisms that might correspond to observed changes in patient function. On the other hand, group differences in average quadriceps activation were seen in the Stevens-Lapsley *et al.* trial at one month after surgery (82.3% activation in the NMES group, 73.6% in the control group), lending some support to the idea that

NMES may achieve its clinical effects by altering the neural mechanisms underlying quadriceps activation. However, there may be many other measures of muscle physiology and motor control (thus far omitted from all clinical studies of NMES following TKA) that could provide important insights into the possible avenues of NMES effectiveness. For example, although patients are known to adopt altered movement strategies following TKA,[60-65] none of the recent NMES studies made assessments of lower extremity kinematics or limb loading behavior. Future studies should therefore lend careful consideration to the measures that best capture pertinent aspects of muscle function following TKA while drawing from all domains of the International Classification of Functioning (body structure and function, activity and participation).

In spite of the methodological limitations present in recent studies of NMES following TKA, evidence now exists from two trials suggesting NMES combined with supervised physical therapy is more effective for improving outcomes following TKA, compared to supervised physical therapy alone.[52, 53] Upon thoughtful examination of these two studies and the specific treatment parameters adopted, several key avenues for promoting the therapeutic effectiveness of NMES might be identified.

NMES should occur early after TKA.

In the study by Petterson *et al.*, which failed to show a therapeutic effect of NMES following TKA, the intervention was not initiated until the fourth post-operative week. The two studies that demonstrated effectiveness of NMES - perhaps in recognition of more recent data regarding the time course and extent of activation deficits - elected to initiate the intervention on the second post-operative day. Importantly, in these two trials, the results clearly indicate that NMES helped to attenuate the dramatic loss in quadriceps strength and physical functioning that typically occurs as a result of surgery. Indeed, after the initial postoperative assessment (occurring approximately 1-2 months following surgery) the differences between NMES groups and control groups were most marked, and these differences did not appear to continue to expand beyond this time-point (although in the trial by Stevens-Lapsley *et al.*, differences between groups persisted for the year-long study duration). In general these findings are consistent with the idea that NMES supplements voluntary activation and may be most effective when activation deficits are pronounced. Thus, there may be a critical time window during which the therapeutic benefits of NMES can be realized, although further research is required to better define the precise parameters of this window, including the extent to which it spans the perioperative period.

Higher overall volume of NMES may be required to achieve a treatment effect.

Another important difference between the study by Petterson *et al.* and the studies by Stevens-Lapsley *et al.* and Avramidis *et al.* was the regularity of NMES intervention. Petterson *et al.* delivered NMES 2-3 times per week in the context of a supervised physical therapy session (for approximately 15 minutes each session), whereas Avramidis *et al.* and Stevens-Lapsley *et al.* instructed patients on how to self-administer NMES on a daily basis (approximately 4 hours per day for Avrimidis *et al.*; approximately 30 minutes per day for Stevens-Lapsley *et al.*). Thus, the overall volume of NMES received by patients in the Petterson *et al.* study was at most 3 to 4.5 hours total, whereas the patients in the study by Avramidis *et al.* received a maximum of approximately 164 hours of NMES over the course of the study, and the patients in the study by Stevens-Lapsley *et al.* received a maximum of approximately 20 hours of intervention time. When duty cycles are included in these estimates, differences between studies appear to be further exaggerated; participants in the study by Avramidis *et al.* may have received upwards of 80 hours of actual NMES stimulation to the quadriceps over the course of the intervention, whereas participants in the study by Petterson *et al.* received as little as 20 minutes of total quadriceps contraction time during the 6-week intervention.

It is important to note that actual NMES times in all studies are likely to be much shorter than what was reported in the intervention parameters. Of all the studies, Stevens-Lapsley *et al.* were the only group to report adherence rates, with 77.4% of patients demonstrating greater than 80% adherence to the NMES program. Although the overall amount of NMES may be critical to its effectiveness, we lack the necessary information to form a full understanding of the dose-response relationship that exists between NMES and strength improvements following TKA. The therapeutic validity of future studies may be enhanced with an accurate reporting of NMES stimulation times achieved during intervention.

Intensity of NMES appears to be critical to achieving strength gains.

In addition to the overall stimulation times achieved during NMES intervention, the intensity of stimulation is likely to play a role in the effectiveness of treatment. Although most of the recent NMES clinical trials stated that intensity was determined by maximum patient tolerance, only Stevens-Lapsley *et al.* reported the corresponding torque produced by study participants during the maximally tolerable NMES-induced quadriceps contraction. As mentioned, NMES intensities varied widely, from 1.6% to 76.7% of preoperative MVIC (mean = approximately 17% MVIC). A recent secondary analysis of this data suggested that NMES training intensity was strongly correlated with quadriceps strength gains, especially early after surgery.[66] Nevertheless, NMES is known to activate nociceptors,[67] and the extent to which this causes a perception of discomfort that limits training intensity is likely to vary substantially across individuals.

Several key factors may allow clinicians to optimize patient comfort in order to maximize NMES stimulator intensity. First of all, large electrodes should be used, so that electrical stimulation can be applied to a broad area of the quadriceps muscle and the overall density of NMES current can thereby be reduced. In the studies by Stevens-Lapsley *et al.* and Petterson *et al.*, the total surface area of the electrodes used for NMES stimulation was approximately 193.6 cm^2, whereas the study by Avrimidis *et al.* utilized an area roughly half as large (approximately 98 cm^2). Patients should also be taught to safely operate the stimulator to facilitate self-efficacy and control over the levels of discomfort induced by NMES stimulation. Using a pen to mark electrode location for individual patients may allow them to maintain appropriate electrode placement from session to session.

There is a risk of injury with any rehabilitation program following TKA surgery. However, the use of high intensity NMES has not been associated with any increase in injury rates. Furthermore, joint and thigh edema after TKA has the effect of increasing electrical impedance, such that NMES often delivers a lower intensity stimulus to the muscle (and is thus more comfortable) immediately following surgery. Patients should be thoroughly screened for appropriate cognitive function and contraindications to NMES [68] - most notably the presence of pacemakers or implantable cardioverter defibrillators (ICDs) [69, 70] - so that eligible patients can be reassured of the safety of the intervention and instructed to maximize intensity to optimize the potential for strength improvements.

NMES is most effective as an adjunct to supervised exercise.

Finally, it is important to note that three of the four studies included NMES as an adjunct therapy, measuring its effectiveness against rehabilitation programs that included some form of resistance training. In the study by Petterson *et al.*, the overall effectiveness of this exercise-based intervention was preliminarily demonstrated via a comparison between clinical trial participants and a cohort of patients who refused to participate but who were otherwise eligible for the study. Patients in the clinical trial, regardless of group assignment, demonstrated significantly greater improvements in strength and physical performance compared to patients receiving standard of care rehabilitation. Although factors such as selection bias could also have contributed to these observed differences, it is worth noting that the exercise program adopted by study participants was relatively rigorous; exercises were prescribed and progressed based on individual patients' 10-repetition maximum.

In the study by Levine *et al.*, non-inferiority was demonstrated between supervised physical therapy and unsupervised NMES. However, based on the results obtained by Petterson *et al.*, as well as the performance data of patients in the trials that included both high doses of NMES and rigorous programs of supervised physical therapy, it seems possible that greater improvements in strength might be realized when treatment modalities are combined. The effectiveness of a progressive resistance training intervention for improving strength and function following TKA has yet to be established, and the optimal time course over which to apply NMES and volitional strengthening interventions should be a topic of continued investigation.

NMES following total hip arthroplasty

Although not the primary focus of this manuscript, NMES of the quadriceps has also been studied in two small, randomized controlled trials for patients undergoing total hip arthroplasty (THA).[71, 72] Recent observational studies suggest that quadriceps weakness is commonly seen following THA,[73] albeit to a lesser degree than is typically seen following TKA. Furthermore, the mechanisms underlying quadriceps weakness surrounding THA have not been examined to the same extent as in the TKA population. The magnitude and time course of quadriceps activation deficits following THA would benefit from further study, and the overall influence of quadriceps weakness on functional prognosis after THA remains a topic of ongoing research. Although THA and TKA surgeries share certain similarities (both procedures are commonly performed to address joint pain in older adults with osteoarthritis), they are in fact different procedures, performed on different surgical populations with different comorbidity profiles,[74] and the postoperative rehabilitation strategies likely deserve separate consideration.

Nevertheless, quadriceps NMES may have some benefits after THA. The results of the trial by Suetta *et al.* (2004) showed that patients receiving NMES and patients receiving a resistance training intervention following THA demonstrated improved functional performance (walking speed, stair climbing speed, sit-to-stand ability) compared to patients receiving a standard rehabilitation program.[71] However, in this study, only the resistance training group showed improved quadriceps strength and cross-sectional area beyond pre-surgical levels by 12 weeks post-surgery. The results of the trial by Gremeaux *et al.* (2008) suggested that the addition of NMES bilaterally to the quadriceps and triceps surae produced greater maximal isometric strength gains in the quadriceps, but did not improve walking performance on the 6MWT or the 200m fast walk test at 9 weeks postsurgery.[72] Thus, the current state of evidence for NMES following THA suggests conflicting results. Given the paucity of information on the mechanisms of muscle weakness following THA and subsequent strength-function relationships, and considering the differences in NMES protocols used, it is difficult to synthesize the results from these two small clinical trials. Continued investigation into the use of NMES as a strength training modality in THA is warranted.

Conclusions

The use of NMES as a strengthening modality following TKA is appealing for a few reasons: 1) patients often possess deficits in voluntary activation immediately after surgery that preclude volitional strength training at the appropriate intensities, 2) NMES can be self-administered and performed effectively on a daily basis, and 3) at the appropriate dosages, NMES appears to offer the potential for dramatic and persistent improvements in strength, physical functioning, and overall physical health. Several recent controlled studies have examined the effectiveness of NMES for improving strength and function following TKA. These studies are not without their flaws in methodological quality and therapeutic validity. However, a careful examination of the study parameters and results suggests that high intensity NMES, performed regularly during the immediate postoperative phase, may help to attenuate dramatic losses in quadriceps strength immediately following TKA. The long-term impact of weakness due to disuse atrophy resulting from early post-operative quadriceps muscle activation deficits may therefore be reduced, and patients may retain the potential for greater overall improvements in strength and function. Future research should seek to refine our understanding of the NMES parameters - including the timing, frequency, duration and intensity - required to optimize functional recovery for patients undergoing TKA.

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