

Femoral quadriceps neuromuscular electrical stimulation after total knee arthroplasty: a systematic review

Estimulação elétrica neuromuscular do quadríceps após artroplastia total de joelho: uma revisão sistemática

Helena Bruna Bettoni Volpato¹, Paulo Szego¹, Mario Lenza¹, Silvia Lefone Milan¹, Claudia Talerman¹, Mario Ferretti¹

ABSTRACT

The purpose of this study was to evaluate the effects of neuromuscular electrical stimulation in patients submitted to total knee arthroplasty. This was a systematic review with no language or publication status restriction. Our search was made in Cochrane Library, MEDLINE, Embase and LILACS. Randomized or quasi-randomized clinical trials evaluating neuromuscular electrical stimulation after total knee arthroplasty were included. Four studies with moderate risk of bias and low statistical power were included, totalizing 376 participants. There was no statistically significant difference in knee function, pain and range of motion during 12 month follow-up. This review concluded that neuromuscular electrical stimulation was less effective than traditional rehabilitation in function, muscular strength and range of motion. However, this technique was useful for quadriceps activation during the first days after surgery.

Keywords: Arthroplasty, replacement, knee; Knee prosthesis; Knee joint; Osteoarthritis; Physical therapy modalities; Electric stimulation; Quadriceps muscle

RESUMO

O objetivo deste estudo foi avaliar os efeitos da estimulação elétrica neuromuscular em pacientes submetidos à artroplastia total de joelho. Esta foi uma revisão sistemática sem restrição de idioma ou *status* de publicação. Nossa pesquisa foi realizada na biblioteca Cochrane, MEDLINE, Embase e LILACS. Foram incluídos ensaios clínicos randomizados ou quase-randomizados, avaliando a estimulação elétrica neuromuscular após a artroplastia total de joelho. Quatro estudos com risco de viés moderado e de baixo poder estatístico foram incluídos, totalizando 376 participantes. Não houve diferença estatisticamente significativa na função do joelho, dor e amplitude de movimento durante 12 meses de seguimento. Esta avaliação concluiu que a estimulação

elétrica neuromuscular foi menos eficaz do que a reabilitação tradicional na função, força muscular e amplitude de movimento. No entanto, essa técnica é útil para a ativação do quadríceps durante os primeiros dias após a cirurgia.

Descritores: Artroplastia de joelho; Prótese do joelho; Articulação do joelho; Osteoartrite; Modalidades de fisioterapia; Estimulação elétrica; Músculo quadríceps

INTRODUCTION

Osteoarthritis is a degenerative joint disease characterized by reduction of articular cartilage in some areas, and can be related to bone hypertrophy (osteophytes and subchondral bone sclerosis) resulting from biochemical alterations and biomechanical stresses. It is estimated that 75% of the population aged over 65 years is affected by this disease, with a higher prevalence in women, mostly at the knee joint.^(1,2)

All the above-mentioned alterations result in quality of life reduction due to functional limitation. Knee arthroplasty is a common and effective intervention for knee osteoarthritis treatment when the clinical therapy is unsuccessful. Its applicability grew 73% at the last 10 years and it is expected that its indication rises more than 600% (3.48 million procedures) until 2030.⁽³⁾

Such percent growth in total knee arthroplasty (TKA), first introduced in the 1960s, is due to pain relief and range of motion (ROM) gain. TKA main goal is to reestablish the patient's joint compromised function. This is why TKA is considered as one of the most

¹ Hospital Israelita Albert Einstein, São Paulo, SP, Brazil.

Corresponding author: Mario Ferretti – Avenida Albert Einstein 627/701, 3rd floor, building A1 – Morumbi – Zip code: 052652-900 – São Paulo, SP, Brazil – Phone: (55 11) 3078-7945
E-mail: mario.ferretti@einstein.br

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important surgery developments of this century. On the United States alone, currently nearly 140 thousand TKAs are performed each year. However, surgery itself is not capable to restore the patient's complete functionality. Physical therapy is an integral part of treatment, yielding the best results regarding postoperative pain, physical function and quality of life.⁽⁴⁾

As such, early rehabilitation start following TKA significantly benefits joint mobility and muscle stretch gain, favoring important quality of life gains and preventing postoperative complications. Apart from the primary benefits, the immediate rehabilitation could reduce hospital stay and improve the joint functional ability in the short and medium-run.⁽⁵⁾ Another study showed joint pain relief and gait velocity and cadence improvement.⁽⁶⁾

Labraca et al.⁽²⁾ showed that, despite the few scientific evidences, isometric and isotonic exercises designed for quadriceps strengthening between zero and 30° of flexion, ROM gain and inferior limb muscle stretching are usually employed with good results.

Other studies showed that postoperative weakness, muscle atrophy and knee function alterations are common during the first 4 weeks after surgery, causing a quadriceps strength *déficit* compared to the contralateral limb that reaches a 18% reduction.^(7,8)

Although the neurophysiologic mechanisms for quadriceps muscle voluntary activation *déficits* are not fully understood, spinal reflex activity from swelling or pain in the knee joint may change afferent input from the injured joint and result in diminished efferent motor drive to the quadriceps muscle (also referred to as “reflex inhibition”) that reduces muscle strength.^(9,10)

One of the measures to reduce voluntary activation *déficits* and prevent muscle atrophy after TKA is the neuromuscular electrical stimulation (NMES) as an adjuvant restoring normal knee function.⁽⁹⁾

OBJECTIVE

Based on the previously mentioned literature, the objective of this review was to systematically evaluate the effects (benefits and harms) of neuromuscular electrical stimulation in patients who underwent to total knee arthroplasty.

METHODS

Data sources and searches

Institutional review board approval (number 1,593-12) was obtained to perform this systematic review. The study was registered at - International Prospective Register of Systematic Reviews (Prospero), protocol CRD42013005491.

Types of studies

We included randomized or quasi-randomized (in which participants therapy-allocation was not strictly random, *i.e.*, using hospital register number, alternation, medical file number etc.) clinical trials evaluating physical therapy interventions with NMES after TKA.

Types of participants

We included studies that evaluated (skeletally mature) adults who underwent rehabilitation with NMES after TKA.

Types of intervention

All physical therapy interventions used at post-TKA treatment associated with NMES were considered. We compared NMES with physical therapy rehabilitation.

Studies comparing non-physical therapy-related or specific formation rehabilitation techniques (including Mulligan, Maitland, Pilates etc.) were excluded.

Types of outcome measures

Primary outcomes included function or disability evaluation. The inferior limb functional outcome was evaluated according validated questionnaires, such as the knee dysfunction-specific Lysholm Knee Scoring Scale,⁽¹¹⁾ including joint symptoms evaluation.

Quality of life (evaluated by 36-Item Short Form Health Survey – SF-36),⁽¹²⁾ and treatment failure (prosthesis loosening) were also observed.

Secondary outcomes included pain, with pain reports evaluated according to validated scales, such as Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS). Range of motion was checked by assessing the joint mobility degrees for both knee flexion and extension. Return to previous activities (work, sport, daily life activities etc.), as well as hospitalization time and costs were considered part of secondary outcomes.

Primary outcomes were evaluated at the following periods: short-term (up to 4 months of treatment) and long-term (over 4 months of treatment) follow-up.

Research methods for studies identification

Electronic searches

Our search was performed at Cochrane Central Register of Controlled Trials - CENTRAL (The Cochrane Library, August 2013 edition), MEDLINE (from 1966 up to August 2013), Embase (from 1974 up to August 2013) and LILACS (from 1982 up to August 2013). We also searched Current Controlled Trials (at

<http://www.controlled-trials.com>) and Clinical Trials (at www.clinicaltrials.gov) for ongoing and recently completed studies. There were no language or publication status-based restrictions.

At MEDLINE (PubMed), a specific filter (sensitivity and maximum precision version) for randomized clinical trials identification was combined to a specific subject strategy.⁽¹³⁾ Search strategies were also performed at The Cochrane Library (Wiley InterScience), Embase (Elsevier) and LILACS (Bireme) as described in appendix 1.

Searching other resources

We checked the reference lists of articles and reviews for possible relevant studies.

Study selection

Two authors independently selected potential eligible titles and abstracts to be included on this review and extracted data using pre-piloted form. Any disagreements were resolved by discussion and, when necessary, with adjudication by a third author. Authors were not blinded to journal and/or authors.

Data extraction and quality assessment

Data extraction and management

Two authors collected the following data using a pre-piloted data extraction form: study methodology characteristics, including study design and duration and the protocol publication prior patient recruitment; financing sources and register details; study participants characteristics, with study site, number of enrolled participants, number of evaluated participants, inclusion criteria, exclusion criteria, participants' age, prosthesis types and surgical techniques; study intervention characteristics, including intervention time, physical therapy intervention and other co-intervention types; study result characteristics, including follow-up time, loss at follow-up and outcome measures; and methodological domains, as described below at the risk of bias evaluation section. Any discrepancies were settled by a third reviewer. Two review authors inputted the data at Review Manager™.

Assessment of risk of bias in the included studies

The risk of bias of the included studies was independently evaluated by two authors. As recommended by The Cochrane Collaboration's "Risk of bias" tool,⁽¹⁴⁾ the

following domains were assessed: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; other bias (*e.g.*, great imbalance between participants groups and risk of bias associated with testers and other caretakers' inexperience).

Each individual criterion was deemed as presenting low risk of bias, high risk of bias and uncertain risk of bias (lack of information or uncertainties regarding potential bias). Discrepancies between authors were solved based on a consensus.

Data synthesis and analysis

Measures of treatment effect

The risk ratio with a 95% confidence interval (95%CI) was calculated for dichotomous variables. Continuous variables results were expressed as mean differences (MD) with 95%CI.

Unit of analysis issues

At the studies included in this review, randomization was based on individual participants. Exceptionally, as in clinical trials including patients with bilateral knee prostheses, data may have been laterally evaluated rather than by individual patients. During the analysis of questions lacking proper corrections, the presentation of such clinical trials data was considered only when discrepancies between analysis units and randomization were small. After data compilation, a sensitivity analysis was performed to examine the effects of the incorrectly evaluated clinical trials in the studies correctly addressed.

Dealing with missing data

The data on outcome were extracted for all randomized patients. When required, the primary study authors were contacted to request missing data, with participant number, sampling loss details, uncertainty measures (standard deviation or error) or number of events.

The standard deviation of continuous variables, with no report of such figure, was calculated using p value and values (95CI%).⁽¹⁴⁾ The impossibility of sampling loss data obtainment was described at the risk of bias table, including a discussion regarding the potential influence of such data at the results and conclusions of the present review. Sensitivity analysis was applied in order to explore these missing data effects.⁽¹⁵⁾

Assessment of heterogeneity

We assessed the heterogeneity of estimate effects between the included studies by visual inspection of the forest plot and using the I^2 statistic.

We quantified the possible magnitude of inconsistency (*i.e.* heterogeneity) across studies, using the I^2 statistic with a rough guide for interpretation as follows: zero to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity.⁽¹⁴⁾ In cases of considerable heterogeneity (defined as I^2 75%), we explored the data further by comparing the characteristics of individual studies and conducting subgroup analyses.

Assessment of reporting biases

For meta-analysis with more than ten studies, primary outcomes graphs were drawn in order to evaluate the potential publication bias (small studies effects). The presence of bias was also evaluated in small studies, to verify if random intervention events were more beneficial compared to fixed events estimative.⁽¹⁶⁾

Data synthesis

When appropriate, results of comparable groups of studies were pooled in meta-analysis using the random-effects model as a default. For dichotomous outcomes, RR and 95%CI were calculated. When two or more studies presented continuous data from the same validated instrument of evaluation using the same units of measure, data were pooled as a MD with 95%CI. When primary studies state the same variable using different instruments and different units of measure, we used the standardized mean difference with 95%CI.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis for following demographics was planned: age (adolescents, adults and people older than 65); type of surgical intervention TKA; and rehabilitation start (outpatient and inpatient).

Sensitivity analysis

We planned sensitivity analyses to measure the effects of including trials at risk of selection bias (inadequate or unclear allocation concealment) or detection bias (inadequate or unclear blinding of outcome assessor). We also planned to assess the presence of small study bias (*i.e.* intervention effect is more beneficial in smaller studies) in the meta-analysis by comparing the fixed-

effect estimate with the random-effects estimate for primary outcomes.

‘Summary of findings’ tables and assessment of the quality of the evidence

When there is sufficient evidence in future to merit the preparation of summary of findings tables, we will develop these for the main comparisons. We used the GRADE approach to assess the quality of evidence related to each of the key outcomes listed in the types of outcome measures.⁽¹⁷⁾

RESULTS

Search results

The search strategy (concluded in August 2013) identified a total of 584 registers at the following current databases: Cochrane Library (129), PubMed (166), Embase (143), LILACS (130), Clinical Trials (11) and Controlled Trials (5).

The search led to the identification of 18 potentially eligible studies, from which the complete papers were retrieved. A total of four studies, published between 1994 and 2013, were included on the review.⁽¹⁸⁻²¹⁾

Overall, there were four included studies, eight excluded studies and six ongoing studies (Figure 1).

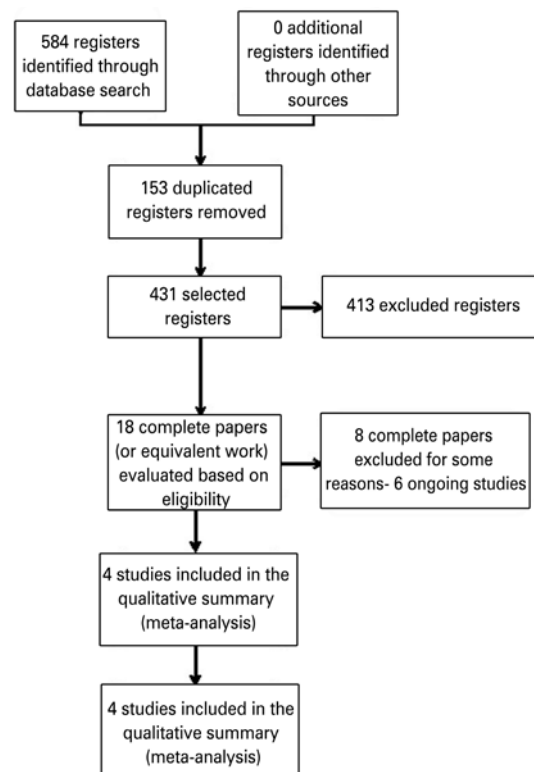


Figure 1. Study flowchart

Included studies

This review was based on four randomized clinical trials: Gotlin et al.,⁽¹⁸⁾ Levine et al.,⁽¹⁹⁾ Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ (all studies presented in English). These trials were found at PubMed, Cochrane Library and Embase. Included studies details are specified at appendix 2.

Study design

Gotlin et al.,⁽¹⁸⁾ Levine et al.,⁽¹⁹⁾ Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ were single-center controlled randomized studies. All studies compared two groups undergoing the same interventions (exercises *versus* exercises and NMES). Gotlin et al.⁽¹⁸⁾ evaluated exercises and continuous passive motion (Control Group) *versus* exercises, continuous passive motion and NMES (experimental group).

Participants

The four studies included trials totalized 376 participants.

Age and sex

Gotlin et al.⁽¹⁸⁾ described that mean age was 64.8 years in the exercise group (control) and 66.2 years in the NMES plus exercise group (intervention). The Control Group comprised 16 women and 15 men, and the intervention group comprised 20 women and 15 men. In Levine et al.,⁽¹⁹⁾ the mean age was 65.1 years in the Control Group, and 68.1 years in the intervention group. The Control Group comprised 21 women and 13 men, and the intervention group was composed of 25 women and 7 men. Petterson et al.⁽²⁰⁾ reported that the Control Group were composed of 45 woman and 55 were men with mean age of 65.2 years-old. In the intervention group, 47 participants were women and 53 were men, presenting mean age between sexes of 65.3 years-old. In Stevens-Lapsley et al.,⁽²¹⁾ the sample consisted of 16 women and 15 men in the Control Group and 20 women and 15 men in the intervention group, presenting mean age between sexes of 64.8 years-old for the Control Group and 66.2 years-old for the intervention group.

All participants, in all trials, held a unilateral or bilateral knee osteoarthritis diagnosis. None of the studies described the classification or TKA previous treatment.

Interventions

The included studies were grouped according to the interventions analyzed.

Gotlin et al.⁽¹⁸⁾ analyzed the effects of exercises and continuous passive motion (Control Group) *versus* exercises, continuous passive motion and NMES (experimental group) in 40 patients. Levine et al.⁽¹⁹⁾ compared a muscle strengthening program and knee ROM gain *versus* NMES associated only to knee ROM exercises in 70 participants. Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ compared a progressive muscle (quadriceps) strengthening program *versus* NMES associated with progressive muscle strengthening, both of early start (immediate postoperative), in 266 participants.

Primary outcomes

Function or deficiency

Knee function was evaluated in three studies.⁽¹⁹⁻²¹⁾ Levine et al.⁽¹⁹⁾ used Timed Up and Go (TUG), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire and Knee Society Score (KSS) to measure the joint function. Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ used validated instruments – Timed Up and Go (TUG) Stair Climbing Test (SCT), 6-Minute Walk (6MW) – to evaluate knee functional compromise. Stevens-Lapsley et al.⁽²¹⁾ also used the WOMAC questionnaire. In addition to these instruments, Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ evaluated quadriceps muscle strength using dynamometry.

Quality of life

Gotlin et al.⁽¹⁸⁾ and Levine et al.⁽¹⁹⁾ did not measure this endpoint. Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ evaluated the quality of life using SF-36.

Treatment failure

All included trials reported no treatment failures.

Secondary outcome

Pain

Pain was evaluated in three studies.⁽¹⁹⁻²¹⁾ Levine et al.⁽¹⁹⁾ used the validated score from KSS to measure pain, and Petterson et al.⁽²⁰⁾ used a validated score (Knee Outcome Survey - KOS and Activities of Daily Living Scale - ADLS); Stevens-Lapsley et al.⁽²¹⁾ measured individuals pain complaint applying a numeric visual scale.

Range of motion

In Gotlin et al.,⁽¹⁸⁾ Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ studies were evaluated through goniometry. Levine et al.⁽¹⁹⁾ also evaluated their participants' knee ROM, but did not report which instrument was used to measure this outcome.

Excluded studies

Eight papers were excluded for not meeting the inclusion criteria. The reasons for exclusion are presented in chart 1.

Ongoing studies

Our search for ongoing studies resulted in 16 papers on Clinical Trials and Current Controlled Trials. Ten studies were excluded for not meeting our inclusion criteria or being irrelevant. We included: ISRCTN89785408, ISRCTN50117467, NCT01096524, NCT01548040, NCT00224913 and NCT01844193 (Appendix 3).

Risk of bias in the included studies

All included trials had methodological flaws, rendering them at moderate risk of bias (Figure 2).

Allocation (selection bias)

Gotlin et al.,⁽¹⁸⁾ Levine et al.,⁽¹⁹⁾ Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ did not report how the random sequence generation was performed.

Concealment of allocation before assignment was not described in any study, preventing its appreciation (unclear).

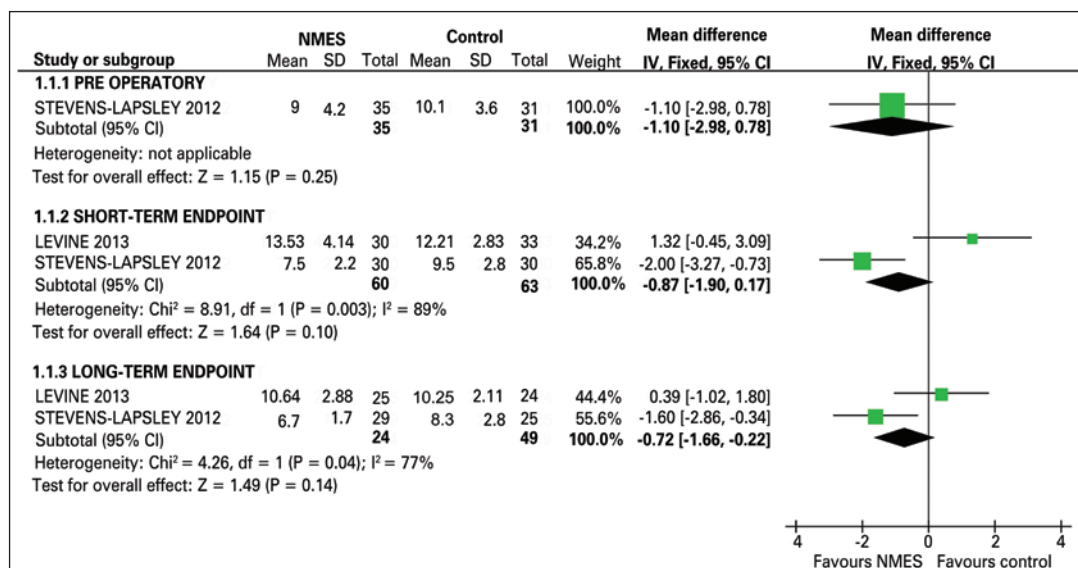
Blinding (performance bias and detection bias)

All trials were judged to be at high risk of performance and detection bias. As they all compared physical therapy interventions, it was not possible to blind treatment providers. No trials included sham intervention; therefore participants were not blinded. It may have

Chart 1. Characteristics of the excluded studies

Study	Reason for exclusion
Petterson et al. ⁽²²⁾	Case report
Mintken et al. ⁽²³⁾	Case report
Stevens et al. ⁽⁹⁾	Case series
Stevens-Lapsley et al. ⁽²⁴⁾	Observational study
Bade et al. ⁽²⁵⁾	Literature review
Saleh et al. ⁽²⁶⁾	Literature review
Walls et al. ⁽²⁷⁾	NMES use only in the pre-operative period
Stevens et al. ⁽²⁸⁾	Incomplete unpublished data

NMES: neuromuscular electrical stimulation.



NMES:neuromuscular electrical stimulation. SD: standard deviation; IV:inverse variance; 95%CI: 95% confidence interval.

Figure 2. Risk of bias chart

been possible to blind outcome assessors; however, only two trials mentioned assessor blinding.⁽¹⁸⁻²⁰⁾

Incomplete outcome data (attrition bias)

Trials with 80% or more participants completing follow-up and those whose losses were balanced between intervention groups were deemed as presenting low risk of bias. All included trials⁽¹⁸⁻²¹⁾ were considered as presenting low risk of bias.

Selective report (reporting bias)

Three studies⁽¹⁹⁻²¹⁾ were considered as presenting low risk of bias, since their protocols and pre-specified outcomes were available. On the other hand, Gotlin et al.⁽¹⁸⁾ was considered as high risk of bias, since it did not present a specified protocol.

Additional potential bias sources

Gotlin et al.,⁽¹⁸⁾ Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ trials seem to be free from additional biases. Only Levine et al.⁽¹⁹⁾ was considered as high risk of bias, since it not presented a NMES protocol.

Effects of interventions

The included studies evaluated the following outcomes: function or disability, ROM, quality of life and treatment failure. Additional outcomes planned in our protocol were not evaluated due to insufficient data.

Comparison

Neuromuscular electrical stimulation *versus* exercises (with or without continuous passive motion) starting up to the first postoperative week.

Function or disability

Function measures were analyzed and made available in the following sequence: TUG, 6MW, SCT, quadriceps activation, femoral quadriceps strength, and WOMAC.

Timed Up and Go

In Levine et al.,⁽¹⁹⁾ there were no significant differences in both the short-term (MD: 1.32; 95%CI: -0.45-3.09) and long-term endpoint (MD: 0.39; 95%CI: -1.02-1.80). In the Stevens-Lapsley et al.⁽²¹⁾ study, we noted a statistically significant difference favoring NMES in both the short-term (MD: -2.00; 95%CI: -3.27- -0.73) and long-term endpoint (MD: -1.60; 95%CI: -2.86- -0.34). Studies data grouping did not show any statistically significant difference between the two intervention groups (MD: -0.87; 95%CI: -1.90-0.17), (MD: -0.72; 95%CI: -1.66-0.22) at short-term and long-term endpoint, respectively (Figure 3).

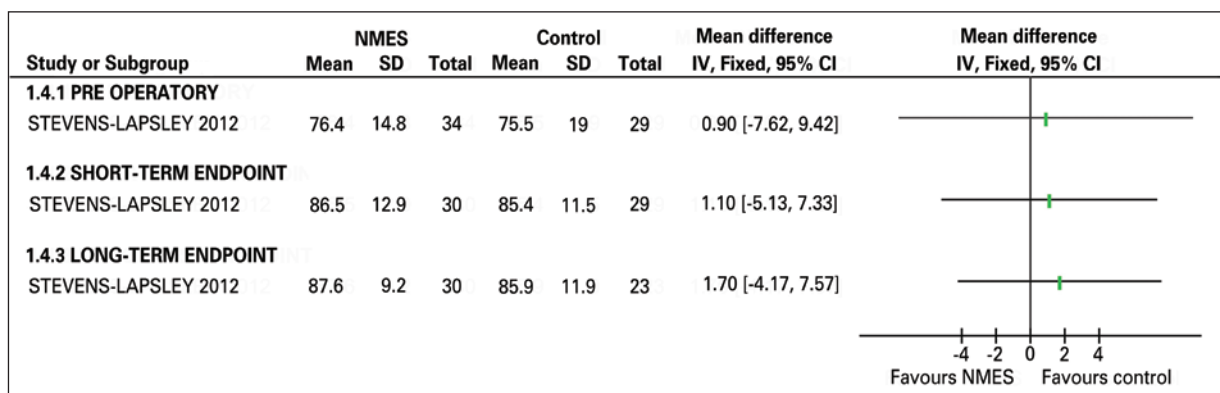
Petterson et al.⁽²⁰⁾ reported no statistically significant difference ($p>0.08$).

6-minute walk test

Difference between groups in Stevens-Lapsley et al.⁽²¹⁾ study marginally favored control at the short-term endpoint (MD: 62.60; 95%CI: 15.51-109.69). At long-term endpoint, no difference between groups was noted (MD: 46.80; 95%CI: -0.53-94.13). No statistically significant difference was reported by Petterson et al.⁽²⁰⁾ ($p>0.08$).

Stair Climbing Test

Petterson et al.⁽²⁰⁾ report no significant difference for this outcome at the short-term or long-term endpoint ($p>0.08$). At Stevens-Lapsley et al.⁽²¹⁾, no statistically significant difference between the two groups - NMES and exercises (MD: -2.70; 95%CI: -6.40-1.00), (MD: -3.30; 95%CI: -7.27-0.67) was noted in both short-term and long-term endpoint, respectively.



NMES: neuromuscular electrical stimulation. SD: standard deviation; IV: inverse variance; 95%CI: 95% confidence interval.

Figure 3. Timed Up and Go graph

Quadriceps activation (%)

Petterson et al.⁽²⁰⁾ reported the same, with $p > 0.08$. Stevens-Lapsley et al.⁽²¹⁾ reported no statistically significant difference at the short-term endpoint (MD: 1.10; 95%CI: -5.13-7.33) between both groups and at the post-TKA short-term endpoint (MD: 1.70; 95%CI: -4.17-7.57) (Figure 4).

Femoral quadriceps strength (N-m/kg)

Petterson et al.⁽²⁰⁾ also reported the lack of significant difference between groups ($p > 0.08$). No statistically significant differences between the two groups at the short-term (MD: 0.22; 95%CI: -0.02-0.46) and the long-term endpoint (MD: 0.16; 95%CI: -0.09-0.41) were noted at Stevens-Lapsley et al.⁽²¹⁾

Quality of life

The SF-36 questionnaire was used to measure the quality of life during and after the physical therapy intervention in both Petterson et al.⁽²⁰⁾ and Stevens-Lapsley et al.⁽²¹⁾ studies and data were analyzed according to its components.

SF-36 physical component summary

Petterson et al.⁽²⁰⁾ reported no significant difference between groups ($p > 0.08$). Stevens-Lapsley et al.⁽²¹⁾ also reported no statistically significant differences at the short-term (MD: 3.20; 95%CI: -1.50-7.90) and the long-term endpoint (MD: 1.90; 95%CI: -1.97-5.77).

SF-36 mental component summary

Petterson et al.⁽²⁰⁾ reported no significant difference, with $p > 0.08$. At the mental component summary, Stevens-Lapsley et al.⁽²¹⁾ also reported no statistically significant difference in both the short-term (MD: 3.70; 95%CI: -1.55 -8.95) and long-term endpoint (MD: 3.00; 95%CI: -0.39 -6.39).

Quality of life and function

WOMAC questionnaire was used by Levine et al.⁽¹⁹⁾ to measure knee function, with no statistically significant difference between groups in both the short-term (MD: 5.67; 95%CI: -1.88-13.22) and long-term endpoint (MD: 5.81; 95%CI: -3.01-14.63). Stevens-Lapsley et al.⁽²¹⁾ also reported no statistically significant difference in both the short-term (MD: -6.80; 95%CI: -15.04-1.44) and at the long-term endpoint (MD: -4.30; 95%CI: -9.99-1.39). Data pooling showed no statistically significant difference in both the short-term (MD: -0.02; 95%CI: -5.59-5.54) and at the long-term endpoint (MD: -1.33; 95%CI: -6.11 -3.45) between the two intervention groups.

Levine et al.⁽¹⁹⁾ used the KSS questionnaire to check knee function and reported no statistically significant difference in both the short-term (MD: 4.97; 95%CI: -4.65-14.59) and the long-term endpoint (MD: 7.92; 95%CI: -2.29-18.13).

Petterson et al.⁽²⁰⁾ used the KOS questionnaire to measure knee function and also reported no statistically significant difference in both short-term and long-term endpoint ($p > 0.01$).

Treatment failure

All included trials reported no treatment failures.

Pain

None of the included studies individually evaluated this outcome.

Range of motion

Knee flexion

Levine et al.⁽¹⁹⁾ reported no statistically significant difference at short-term (MD: -3.20; 95%CI: -8.52 -2.12) and long-term endpoint (MD: 2.30; 95%CI: -4.25

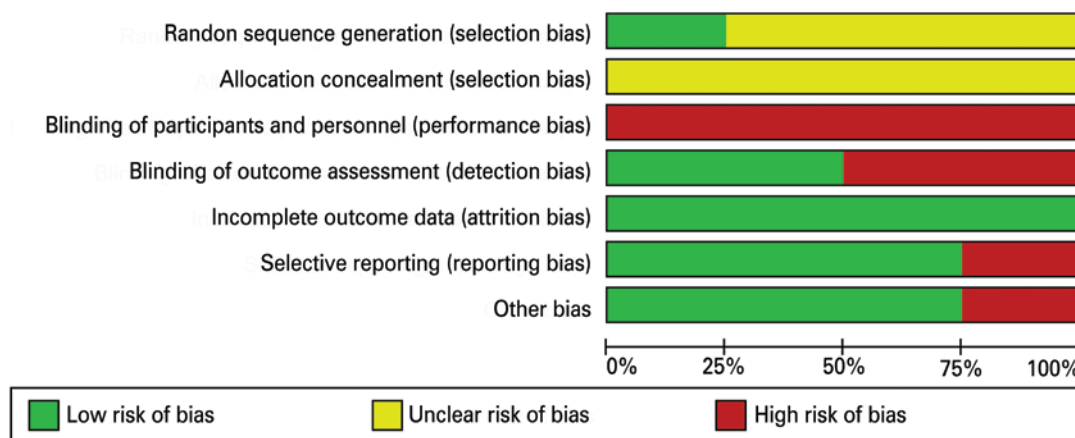


Figure 4. Quadriceps activation chart

-8.85). Stevens-Lapsley et al.⁽²¹⁾ reported no statistically significant difference between groups - NMES and exercises (MD: 2.90; 95%CI: -1.89-7.69 and MD: 2.40; 95%CI: -1.82-6.62) at the short-term and long-term endpoint, respectively. Petterson et al.⁽²⁰⁾ also reported no statistically significant difference ($p>0.01$). Data pooling showed no statistically significant difference between the two intervention groups (MD: 0.17; 95%CI: -3.39-3.73; and MD: 2.37; 95%CI: -1.18-5.92) in both the short-term and long-term endpoint, respectively.

Knee extension

Gotlin et al.⁽¹⁸⁾ and Stevens-Lapsley et al.⁽²¹⁾ reported a statistically significant difference favoring the intervention group compared with the group without intervention in the short-term endpoint (MD: -2.65; 95%CI: -4.05- -1.25 *versus* MD: -2.40; 95%CI -4.09- -0.71) respectively, with no statistically significant difference in the long-term endpoint, that was reported only in the study by Stevens-Lapsley et al.⁽²¹⁾ (MD: -0.60; 95%CI: -2.43-1.23). Levine et al.⁽¹⁹⁾ reported no significant difference in both the short-term endpoint (MD: 0.65; 95%CI -2.00 -3.30) and the long-term endpoint (MD: -0.96; 95%CI: -3.62-1.70). When data were pooled, a statistically significant difference in the short-term endpoint was noted (MD: -2.09; 95%CI: -3.09- -1.09); however, there was no statistically significant difference in the long-term endpoint (MD: -0.72; 95%CI: -2.22-0.79) in both intervention groups.

Petterson et al.⁽²⁰⁾ report no significant difference between both groups during all months of intervention ($p>0.01$).

DISCUSSION

At this review, only randomized clinical trials were included, leading to the analysis of four trials deemed of moderate risk of bias and evaluating kinesiotherapeutic physical therapy interventions compared to NMES with physiotherapy use in 376 participants undergoing TKA.

No evidence indicated if NMES with physiotherapy provided benefits regarding the quality of life. The postoperative treatment with NMES can improve the femoral quadriceps function, but we are not sure about the effectiveness of this intervention, due to the low quality evidence.

Very low evidence from the included trials presented a low general quality resulting from methodological failures, including the lack of allocation concealment and participants and personnel blinding in all trials. However, the quantitative results of this review must be carefully interpreted, requiring confirmation of such

data by evidence derived from high methodological quality trials.

We believe that our search strategy was complete, with no language restriction. However, it is possible that we missed some potentially eligible studies. We tried to contact the included studies' authors in order to obtain some data, but with no success.

We found a systematic review comparing NMES *versus* exercise therapy to treat the quadriceps inhibition after TKA (Monaghan et al.).⁽²⁹⁾ including two randomized and non-randomized clinical trials, and a total of 69 subjects. Our study results are consistent with the Cochrane systematic review results and our conclusion is similar to this publication.

Monaghan et al.⁽²⁹⁾ evaluated NMES use for quadriceps strengthening pre- and post-TKA and reported no significant differences for these outcomes; however, they considered included studies with a high risk of bias due to study design limitations and presented results imprecision, preventing a meta-analysis performance. The authors concluded that the identified studies do not allow any definition regarding NMES pre- or post-TKA.

Monaghan et al.⁽²⁹⁾ also interpreted that participants undergoing quadriceps NMES presented a slight advantage in function improvement and less deficiency than those conservatively treated in the short follow-up, just as we see at the clinical practice and consistent with the findings in Gotlin et al.⁽¹⁸⁾ However, efficacy was reduced at the long-term follow-up.

Therefore, this review is inconclusive about NMES efficacy, and further evidence is required to support or deny its use at quadriceps activation after TKA. The authors are aware that this review subject is the object of an ongoing investigation and could be updated in order to incorporate new evidences.

CONCLUSION

The very low evidences from included studies found on this review do not allow any conclusions regarding neuromuscular stimulation application for quadriceps strengthening with physical therapy before or after total knee replacement. Until now, evidence for neuromuscular stimulation use to quadriceps strengthening in this patient group is unclear. However, it is critical that future studies verify the quadriceps strength pre- and post-neuromuscular stimulation using reliable evaluations and validated tools, as well as a clear description of the applied dose in the study design. It is also of uttermost importance that results be presented appropriately for meta-analysis performance.

ACKNOWLEDGEMENTS

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Appendix 1. Search strategy

PubMed

("arthroplasty, replacement, knee"[MeSH Terms] OR ("knee prosthesis"[MeSH Terms] OR "arthroplasty, replacement, knee"[MeSH Terms]) OR tkr{tw}) OR (Knee knee\${tw} AND ("arthroplasty"[MeSH Terms] OR ("joint prosthesis"[MeSH Terms] OR "arthroplasty, replacement"[MeSH Terms]) OR arthroplast\${tw})) AND ("exercise therapy"[MeSH Terms] OR "physical therapy modalities"[MeSH Terms] OR physiotherap\${tw} OR continuous passive motion{tw} OR cpm{tw} OR therap\${tw} OR exercis\${tw} OR Neuromuscular Electrical Stimulation {tw}) AND (meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl\$ [tw] OR doubl\$ [tw] OR trebl\$ [tw] OR tripl\$ [tw]) AND (mask\$ [tw] OR blind\$ [tw])) OR (placebos [mh] OR placebo\$ [tw] OR random\$ [tw] OR research design [mh:noexp]) NOT (animals [mh] NOT human [mh]))

Cochrane Library

1. MeSH descriptor Arthroplasty, Replacement, Knee explode all trees
2. MeSH descriptor Knee Prosthesis explode all trees
3. tkr:ti,ab
4. (#1 OR #2 OR #3)
5. MeSH descriptor Exercise Therapy explode all trees
6. MeSH descriptor Physical Therapy Modalities explode all trees
7. physical NEXT therap*:ti,ab
8. physiotherap*:ti,ab
9. "continuous passive motion" OR:ti,ab
10. Neuromuscular Electrical Stimulation:ti,ab
11. therapeutic NEAR/3 exercis*:ti,ab
12. (#5 OR #6 OR #7 OR #8 OR #9 OR #10)
13. (#4 AND #12)

Embase

1. Arthroplasty, Replacement, Knee/
2. Knee Prosthesis/
3. tkr.tw.
4. 1 or 2 or 3
5. Exercise Therapy/
6. Physical Therapy Modalities/
7. physiotherap*.tw.
8. Neuromuscular Electrical Stimulation.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. Clinical trial/
12. Randomized controlled trial/
13. Randomization/
14. Randomized controlled trial*.tw.
15. Rct.tw.
16. Random allocation.tw.
17. Randomly allocated.tw.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 10 and 18

LILACS

Artroplastia do Joelho OR joelho [Palavras] and (Serviço Hospitalar de Fisioterapia OR Fisioterapia OR Modalidades de Fisioterapia) [Palavras] *Portuguese for Knee arthroplasty OR knee [Words] and (Physical Therapy Hospital Service OR Physical Therapy OR Physical Therapy Modalities) [Words]*

Appendix 2. Extraction form of the characteristics of the included studies

ID study: Gotlin et al.⁽¹⁸⁾		
Methods	Study design: randomized clinical trial Study duration: not reported Protocol published before patient enrollment: no Trial register details: not reported Financing funds: study conducted by the Insall Scott Kelly Institute for Orthopedic and Sports Medicine; Department of Physical Medicine and Rehabilitation	
Participants	Study site: Department of Physical Medicine and Rehabilitation, New York, United States Number of participants assigned: 40 participants Number of participants assessed: 40 participants Inclusion criteria: surgical indication for total knee arthroplasty by osteoarthritis; both sexes Exclusion criteria: not reported Age: – Exercises group + CPM (mean): 66.58 years-old – Exercises group + NMES + CPM (mean): 64 years-old Classification of osteoarthritis: not reported	
Interventions	Intervention time: not reported Surgical intervention type: TKA unilateral Conservative intervention type: muscle strengthening exercises, stretching, ROM gain and function, NMES Rehabilitation: – Exercises + CPM + NMES group: inpatient rehabilitation started in the first postoperative day with basic exercises (ankle pumps, quadriceps sets, gluteal sets, heel slides, gait training) + CPM up to 45° + activities of daily living training + NMES twice a day, for 1 hour, applied at a frequency of 35Hz, with a ramp time of 3 seconds, beginning at 40° of extension and terminating at maximal passive extension – Exercises group: the same protocol mentioned above was used Other co-interventions: not reported	
Results	Follow-up period: 8 month follow-up period; participants were evaluated before and after surgery Loss at follow-up: there were no losses in the sample in both groups Primary outcomes: active and passive extension knee ROM (goniometry). Secondary outcome: not reported Adverse events measured by: – Short-term follow-up: not reported – Long-term follow-up: not reported	
Notes	None	
Risk of bias table		
Bias	Authors appreciation	Appreciation support
Random sequence generation (selection bias)	Unclear	The generation sequence was not reported
Allocation concealment (selection bias)	Unclear	Not reported
Participants and personnel blinding (performance bias)	High	Participants and personnel were not blinded
Outcome evaluation blinding (bias detection)	Low	Outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low	The authors did not report missing data
Selective report (reporting biases)	High	The authors assessed only passive and active extension and days to hospital discharge during up to eight days of follow-up
Other biases	Low	The study seemed to be free from other biases
Acronyms and abbreviations	CPM: continuous passive motion NMES: neuromuscular electrical stimulation TKA: total knee arthroplasty ROM: range of motion	
Study ID: Levine et al.⁽¹⁹⁾		
Methods	Study design: randomized clinical trial Study duration: not reported Protocol published before patient enrollment: no Trial register details: not reported Financing funds: study conducted by the Forbes Regional Hospital, Monroeville, Pennsylvania, with independent financing funds	
Participants	Study site: Forbes Regional Hospital, Monroeville, Pennsylvania Number of participants assigned: 70 participants	

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Appendix 2. Extraction form of the characteristics of the included studies

ID do estudo: Levine et al.⁽¹⁹⁾		
Participants	<p>Number of participants assessed: 70 participants</p> <p>Inclusion criteria: age above 18 years-old; both sexes; surgical indication for unilateral TKA due to OA</p> <p>Exclusion criteria: admission to an extended care facility, pacemaker or defibrillator, acute trauma or fracture, inability to undergo extended physical therapy; surgical review of previous TKA; inflammatory arthritis; inferior limb ischemia; epilepsy; abdominal or inguinal hernia; cutaneous lesions; neurologic and mental incapacitating dysfunctions.</p> <p>Age:</p> <ul style="list-style-type: none"> – Exercises group (mean): 65.1 years-old – Exercises + NMES group (mean): 68.1 years-old <p>Classification of osteoarthritis: not reported</p>	
Interventions	<p>Intervention time: starting at preoperative period (evaluation by two physical therapists participating in the study), 14 days before surgery. Protocol was used in the first postoperative day until hospital discharge and continued from the first postoperative week until 6 weeks after TKA.</p> <p>Surgical intervention type: unilateral TKA</p> <p>Conservative intervention type: muscle strengthening exercises, ROM gain; NMES</p> <p>Rehabilitation:</p> <ul style="list-style-type: none"> – NMES group: rehabilitation started at the first postoperative day only with knee ROM gain exercises supervised by a physical therapist. After discharge, these patients performed the self-applied NMES without the physical therapist presence up to the 60th postoperative day (Complex Neuromuscular Electrical Stimulator DJO Global, Vista, California). Exercises and NMES protocol were not described by the authors – Exercise group: inpatient rehabilitation started at the first postoperative day with basic exercises. Patients were divided into 5 subgroups, the groups 1 and 2 performed only knee ROM gain exercises and groups 3-5 performed ROM gain and muscle strengthening exercises. All 5 subgroups were supervised by physical therapists. Exercises protocol was not described <p>Other co-interventions: oral analgesic drugs (oxycodone or tramadol) for pain control were used by all groups</p>	
Results	<p>Follow-up period: 6 month follow-up; participants were evaluated 14 days before surgery, and 6 weeks and 6 months after TKA by a physical therapist</p> <p>Loss at follow-up: 70 participants initiated the study and were lost during the 6-month follow-up:</p> <ul style="list-style-type: none"> – Exercises + NMES group – 35 participants, with 4 lost during the 6 month follow-up: <ul style="list-style-type: none"> – Did not complete treatment: 1 patient – Surgical review: none – Contact loss: none – Moved: none – Refused the test: 1 patient – Other medical conditions: 2 participants (mental confusion after surgery) – Exercises group – 35 participants initiated the study, with 9 lost during the 6 month follow-up: <ul style="list-style-type: none"> – Did not complete treatment: 1 participant (distance) – Surgical review: none – Contact loss: none – Moved: none – Refused the test: 8 patients – Other medical conditions: none <p>Primary outcomes:</p> <ul style="list-style-type: none"> – Function knee: TUG – Active knee ROM: goniometry (flexion and extension) – Pain: NVS <p>Secondary outcome:</p> <ul style="list-style-type: none"> – Function: WOMAC and KSS <p>Adverse events measured by:</p> <ul style="list-style-type: none"> – Short-term follow-up: not reported – Long-term follow-up: not reported 	
Notes	None	
Risk of bias table		
Bias	Authors appreciation	Appreciation support
Random sequence generation (selection bias)	Unclear	The generation sequence was not reported
Allocation concealment (selection bias)	Unclear	Not reported
Participants and personnel blinding (performance bias)	High	Participants and personnel were not blinded
Outcome evaluation blinding (bias detection)	High	Outcome assessors were not blinded
Incomplete outcome data (attrition bias)	Low	The authors did not report missing data
Selective report (reporting biases)	Low	Outcomes of interest in the review were reported

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Appendix 2. Extraction form of the characteristics of the included studies

Risk of bias table		
Bias	Authors appreciation	Appreciation support
Other biases	High	No description of NMES (current type, frequency, pulse, application time etc.) and exercises (number of repetitions, frequency per week etc.) protocols
Acronyms and abbreviations	TKA: total knee arthroplasty OA: osteoarthritis NMES: neuromuscular electrical stimulation ROM: range of motion TUG: Timed Up and Go ENV: escala numérica visual WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index KSS: Knee Society Score	
Study ID: Petterson et al.⁽²⁰⁾ (NCT00224913)		
Methods	Study design: randomized clinical trial Study duration: July 2000 to November 2005 Protocol published before patient enrollment: yes Trial register details: clinical trials identification gov: NCT00224913 Supported by NIH (grant R01-HD041055). Financing funds: study conducted by the University of Delaware (community college) non-profit and without other organisms' financial support	
Participants	Study site: physical therapy clinics from the University of Delaware, United States Number of participants assigned: 1,093 participants Number of participants assessed: 200 participants Inclusion criteria: age between 50 a 85 years-old; both sexes; surgical indication for unilateral TKA by OA Exclusion criteria: uncontrolled hypertension; diabetes; BMI >40kg/m ² ; symptomatic OA at the contralateral knee (pain >4 at the 10-point analogic scale); other orthopedic alterations/pathologies on the inferior limbs; neurologic dysfunctions; living outside a 20-mile radius from the clinics. Age: – Exercises group (mean): 65.2 years-old – Exercises + NMES group (mean): 65.3 years-old Classification of osteoarthritis: not reported	
Interventions	Intervention time: 6 weeks of intervention with a segment for 12 month post-TKA evaluation (patients were evaluated at the 3 rd and 12 th month by blinded testers) Surgical intervention type: tricompartmental, cemented TKA with a medial parapatellar surgical approach Conservative intervention type: muscle strengthening exercises and NMES Rehabilitation: – Exercises + NMES group: treatment began 3 to 4 weeks after TKA. The progressive strengthening exercises program associated with NMES was performed 2 or 3 times per week, for 6 weeks, totalizing 12 therapy visits. Therapies targeting knee extension and flexion, patellar mobility, quadriceps strength (2 series of 10 repetitions, progressing to 3 series), pain control, and gait training were included in both groups. NMES consisted of 10 electrically elicited contractions of the quadriceps. Patients were seated in an electromechanical dynamometer at 60° of knee flexion. Two self-adhesive electrodes were placed over the rectus femoris muscle belly proximally and the vastus medialis muscle belly distally. Stimulation was characterized by a 2,500Hz, sinusoidal, alternating waveform current at 50 bursts per second, for 10 seconds, plus a 2 second ramp on time, with an 80-second rest period between contractions. Current amplitude was increased to the patient's maximum tolerance – Exercises group: the same protocol mentioned above was used Other co-interventions: not reported	
Results	Follow-up period: 1 year follow-up period; participants were evaluated at admission and at 3 and 12 months after TKA Loss at follow-up: 51 participants were lost during the 12-month period: – Exercises group – 19 participants were lost in 1 year: – Did not complete treatment: 3 participants – Review: 1 participant – Contact loss: 6 participants – Moved: 3 participants – Refused the test: 3 participants – Other medical conditions: 3 participants – Exercises + NMES group – 32 participants were lost in 1 year: – Did not complete treatment: 16 participants – Review: 2 participants – Contact loss: 4 participants	

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Appendix 2. Extraction form of the characteristics of the included studies

ID do estudo: Petterson et al.⁽²⁰⁾ (NCT00224913)		
Results	<ul style="list-style-type: none"> – Moved: none – Refused the test: 3 participants – Other medical conditions: 7 participants Primary outcomes: <ul style="list-style-type: none"> – Quadriceps muscle strength: dynamometry (isokinetic) – Function knee: TUG, SCT, and 6MW – Active knee ROM: goniometry. Secondary outcome: <ul style="list-style-type: none"> – Quality of life: SF-36 and KOS, ADLS – Pain: KOS, ADLS Adverse events measured by: <ul style="list-style-type: none"> – Short-term follow-up: not reported – Long-term follow-up: not reported 	
Notes	We contacted the authors by e-mail more than once in order to obtain the missing data, but with no response so far	
Risk of bias table		
Bias	Authors appreciation	Appreciation support
Random sequence generation (selection bias)	Unclear	The generation sequence was not reported
Allocation concealment (selection bias)	Unclear	The concealment method was not reported
Participants and personnel blinding (performance bias)	High	Participants and personnel were not blinded
Outcome evaluation blinding (bias detection)	Low	Outcome assessors were blinded
Incomplete outcome data (attrition bias)	Low	Outcome data figure-balanced between intervention groups, with similar reasons for lack of data between groups
Selective report (reporting biases)	Low	The study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that are of interest for this review have been reported in the pre-specified way
Other biases	Low	The study seems to be free from other biases
Acronyms and abbreviations	NIH: <i>National Institutes of Health</i> TKA: total knee arthroplasty OA: osteoarthritis BMI: body mass index NMES: neuromuscular electrical stimulation ROM: range of motion TUG: Timed Up and Go SCT: Stair Climbing Test 6MW: 6-minute Walk SF-36: Short Form Health Survey-36 KOS ADLS KSS: Knee Outcome Survey Activities of Daily Living scale	
ID study: Stevens-Lapsley et al.⁽²¹⁾ (NCT00800254)		
Methods	Study design: randomized clinical trial Study duration: June 2006 to June 2010 Protocol published before patient enrollment: yes. Trial register details: ClinicalTrials.gov Identifier: NCT00800254 Financing funds: study conducted by the University of Colorado Hospital and funded by the National Institute of Aging (K23AG029978) and the American College of Rheumatology	
Participants	Study site: University of Colorado Physical Therapy Clinics, United States Number of participants assigned: 526 participants. Number of participants assessed: 66 participants. Inclusion criteria: age between 50 and 85 years-old; both sexes; surgical indication for unilateral TKA by OA Exclusion criteria: uncontrolled hypertension; uncontrolled diabetes; BMI >35kg/m ² ; symptomatic OA at the contralateral knee (pain >4 at the 10-point analogic scale); other orthopedic alterations/pathologies on the inferior limbs; incapacitating neurologic alterations Age: <ul style="list-style-type: none"> – Exercises group (mean): 65.2 years-old – Exercises group + NMES (mean): 65.3 years-old Lesion classification: not reported	

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Appendix 2. Extraction form of the characteristics of the included studies

ID do estudo: Stevens-Lapsley et al.⁽²¹⁾ (NCT00800254)		
Interventions	<p>Intervention time: from the first to the third postoperative day (inpatient phase) + 30 days (outpatient phase). Patients were evaluated between 1 and 2 weeks before surgery and at 3, 5, 6, 13, 26 and 52 postoperative weeks by non-blinded study testers</p> <p>Surgical intervention type: unilateral TKA by 3 orthopedists from the University of Colorado.</p> <p>Conservative intervention type: muscle strengthening exercises, stretching, ROM gain and function (gait training); NMES</p> <p>Rehabilitation:</p> <ul style="list-style-type: none"> - Exercises + NMES group: inpatient rehabilitation started at the first postoperative day with basic exercises twice a day and continued during the 3 days of hospitalization (the exercises protocol was the same for both groups). After hospital discharge, participants received 6 treatments at home for 2 weeks followed by 10 to 12 outpatient visits. Exercises consisted of knee passive range of motion stretching; patellofemoral mobilization (as needed); incision mobility; cycling ROM; lower-extremity flexibility exercises for the quadriceps, calf, and hamstring muscles; modalities (ice or heat as needed); gait training; and functional training for transfers and stair climbing. For strengthening, both weight-bearing and non-weight-bearing exercises were initiated with 2 sets of 10 repetitions and progressed to 3 sets of 10 repetitions according to the patient's tolerance. A portable Empi 300PV stimulator (Empi Inc, DJO Global) was used for the NMES intervention because this device is equivalent to the VersaStim 380 (Electro-Med) found at the university rehabilitation clinic. During current application, patient was sat on a stable chair with the affected lower limb secured by Velcro straps to allow for approximately 85° of hip flexion and 60° of knee flexion. Self-adherent electrodes were also used (7.6x12.7cm). Electrodes were placed on the distal medial and proximal lateral portions of the anterior thigh and marked to ensure consistent reapplication by the participant. A biphasic current with symmetrical waveform, F: 50Hz, 15", 3-second ramp-up time, 45" T-off, 250-microsecond pulse duration was used. Treatment was instituted 48 hours after surgery, twice a day, for 6 weeks. These patients, after randomization to this group, were able to try the current before for adaptation purposes. - Exercises group: the same protocol mentioned above was used <p>Other co-interventions: not reported</p>	
Results	<p>Follow-up period: 1 year and 1 month follow-up period; participants were evaluated between 1 and 2 weeks before surgery and 3, 5, 6, 13, 26, and 52 weeks after TKA</p> <p>Loss at follow-up: 36 participants initiated the study and were lost during the 12-month period:</p> <ul style="list-style-type: none"> - Exercises + NMES group – 35 participants, with 5 lost in 1 year: <ul style="list-style-type: none"> - Did not complete treatment: 1 patient - Review: none - Contact loss: none - Moved: 1 participant - Refused the test: none - Other medical conditions: 3 participants (infections) - Exercises group – 31 participants initiated the study, and 6 were lost in 1 year <ul style="list-style-type: none"> - Did not complete treatment: 2 participants - Review: 1 participant - Contact loss: none - Moved: 1 participant - Refused the test: none - Other medical conditions: 2 participants (infections) <p>Primary outcomes:</p> <ul style="list-style-type: none"> - Quadriceps muscle strength: dynamometry - Function knee: TUG, SCT, and 6MW - Active knee ROM: goniometry - Pain: NVS <p>Secondary outcome:</p> <ul style="list-style-type: none"> - Quality of life: SF-36 - Function: WOMAC <p>Adverse events measured by:</p> <ul style="list-style-type: none"> - Short-term follow-up: not reported - Long-term follow-up: not reported 	
Notes	None	
Risk of bias table		
Bias	Authors appreciation	Appreciation support
Random sequence generation (selection bias)	Low	Blocked randomization was described with random block sizes of 4, 6, or 8
Allocation concealment (selection bias)	Unclear	The concealment method was not reported
Participants and personnel blinding (performance bias)	High	Participants and personnel were not blinded
Outcome evaluation blinding (bias detection)	High	Outcome assessors were not blinded
Incomplete outcome data (attrition bias)	Low	Outcome data figure-balanced between intervention groups, with similar reasons for lack of data between groups

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Appendix 2. Extraction form of the characteristics of the included studies

		Risk of bias table	
Bias		Authors appreciation	Appreciation support
Selective report (reporting biases)		Low	The study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that are of interest for this review have been reported in the prespecified way
Other biases		Low	The study seems to be free from other biases.
Acronyms and abbreviations	TKA: total knee arthroplasty OA: osteoarthritis BMI: body mass index ROM: range of motion NMES: neuromuscular electrical stimulation PROM: passive range of motion TUG: Timed Up and Go SCT: Stair Climbing Test 6MW: 6-minute Walk SF-36: Short Form Health Survey-36 WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index		

Appendix 3. Ongoing studies characteristics

		ISRCTN89785408
Title	Kneehab™ pre and post total knee replacement surgery	
Methods	Study design: randomized controlled blinded parallel group trial Random sequence generation: not reported Allocation concealment: not reported Masking: not reported	
Participants	Location: Liverpool, United Kingdom Target sample size (n): 200 participants Inclusion criteria: individuals who are scheduled for total knee replacement surgery; individuals who are at least 18 years of age; individuals with a BMI <35; individuals who are walking independently with or without assistive devices; must be able and willing to complete all study, assessments and to be followed for the full course of the study; must be able to read, write and follow instructions in English; must be able and willing to provide informed consent; must be willing and able to attend the additional preoperative assessment Exclusion criteria: individuals who have failed the pre-TKA operative assessment; individuals with a history of foot and/or ankle pathology; individuals with a history of tibial or femoral fractures; individuals with a history of any underlying neurological conditions; individuals with physical conditions which would make them unable to perform study procedures; individuals with a total hip replacement; individuals undergoing revision TKA of the same operated leg; pregnant women or inadequate precautions to prevent pregnancy; diagnosis of a medical condition that would contraindicate treatment with the product, e.g. skin lesions at electrode site; individuals with an active implanted medical device (i.e. pacemaker, pump); individuals with a history of stroke; individuals with a history of neurological disorder that affects lower extremity function (stroke, peripheral neuropathy, Parkinson's disease, multiple sclerosis etc.); individuals with a diagnosis of inflammatory arthritis (rheumatoid arthritis, gout or psoriatic arthritis); individuals with muscle diseases (i.e. muscular dystrophy); visible skin injury or disease on their legs; principal investigator for this study, or member of study staff	
Interventions	Kneehab™ group: 6 weeks before and 6 weeks TKA (30 minutes of NMES twice per day for 12 weeks), plus standard physiotherapy Control group: 12 weeks (6 weeks pre and post) standard physiotherapy	
Results	Primary outcomes: Determine the efficacy of Kneehab™ in promoting early recovery of quadriceps performance in patients recovering from TKA as determined by: – Clinically significant increase in isometric extensor strength compared to controls – Clinically significant reduction in TUG and SCT score compared to controls Secondary outcomes: quality of life measures; health economic outcomes Timing of outcomes measurement: not reported	
Starting date	Main ID: ISRCTN89785408 Anticipate start date: April 12, 2010 Anticipate last date: July 1, 2011 Status: not recruiting. Estimated study completion date: completed	

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Appendix 3. Ongoing studies characteristics

ISRCTN89785408	
Contact information	Name: Dr Alasdair Santini Address: not reported Telephone: +44 (0)151 330 2071 E-mail: not reported Affiliation: Royal Liverpool & Broadgreen University Hospital (UK) and Bio-Medical Research, Ltd. (Ireland) - provide Kneehab™ (NMES) devices
Acronyms and abbreviations	BMI: body mass index TKA: total knee arthroplasty CVA: cerebrovascular accident NMES: neuromuscular electrical stimulation TUG: Timed Up and Go SCT: Stair Climbing Test
Title	Neuromuscular electrical stimulation of the quadriceps muscle: a novel alternative to total knee replacement in the young patient
Methods	Study design: randomized controlled trial Random sequence generation: not reported Allocation concealment: not reported Masking: single-blind
Participants	Location: Dublin, Ireland Target sample size (n): 35 to 40 patients (15 to 20 per study group) Inclusion criteria: male and female patients aged 45 to 55 years old; grade 3 to 4 arthroscopically diagnosed knee arthritis; conservatively managed; ambulatory patients Exclusion criteria: morbid obesity (BMI >40); uncontrolled hypertension; anticoagulant therapy; neurological disorder; other lower limb impairment affecting function including amputation; malignancy; inflammatory arthritis; implanted pacemaker or defibrillator; dermatological conditions affecting the thigh; recent participation in an exercise or strength training program; inability to walk unassisted
Interventions	NMES group: participants will receive specific instruction from a member of the study team on application and logbook recording of the stimulator. The device will be applied to the affected thigh with electrode placement depending on thigh length and girth according to the manufacturer's guidelines. They will also receive written instruction on the device controls and the NMES training program schedule. All NMES sessions will be performed with the subject sitting with their knee flexed to 60 degrees. Wooden strips joined with a 60 degrees bend will be provided to all subjects to assist with positioning throughout the program. They will sit with their feet flat on the ground and their toes against a wall to prevent knee extension caused by the resulting quadriceps contractions, and thus permit isometric training 5 sessions per week (Monday to Friday) for 6 weeks 20 minutes in duration. Participants will be instructed to use the device early in the morning, between 8 and 10 a.m., to minimize muscle fatigue that may occur after normal daily activities. A student from Dublin City University will attend the participants' home on day 8 to ensure the subject is using the device appropriately as well as adhering to the protocol. Telephone communication will occur weekly, on Fridays, with each subject in the intervention group to ensure they are adhering to the protocol. The stimulator has a built-in log that records the total number of completed sessions, total treatment time, and average intensities reached for each channel for the previous 4 sessions. We will document these readings at weeks 2, 4, and 6 Control Group: subjects assigned to the Control Group will receive standard care. They will attend DCU at baseline, and weeks 3, 6, and 12 for quadriceps strength assessments. All functional and clinical evaluations, as well as MRI scanning, self-report questionnaires and muscle biopsies will be performed as in the intervention (NMES) group. They will also receive weekly telecommunication to answer any questions they may have in relation to the study
Results	Primary outcomes: – Function: WOMAC index – Quality of life: SF-36 Secondary outcomes: – Knee ROM – Body mass – Performance outcome measures: 25-m timed walk test; timed SCT; up/down seated test – Radiological evaluation – Quadriceps muscle strength (Torque): Biodex Multi-joint System 3 dynamometer – Complications of muscle biopsy – Muscle sample analysis – Fiber type distribution – Percent fiber type area – Regulatory protein analysis – RNA isolation Timing of outcomes measurement: weeks 1, 3, 6, 12

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Appendix 3. Ongoing studies characteristics

ISRCTN89785408	
Starting date	Main ID: ISRCTN50117467 Date applied: 17th November 2008 Last edited: 8th January 2009 Status: not recruiting Estimated study completion date: completed
Contact information	Name: Mr. Joshua Chong Yew Ong Address: 13 Lock-keepers Walk Royal Canal Park, Dublin, Ireland Telephone: not reported Website: http://www.cappagh.ie/ Affiliation: <ul style="list-style-type: none"> – Cappagh National Orthopaedic Hospital (Ireland) - facilities used to perform clinical assessments, muscle biopsies and MRI scans – Dublin City University (DCU) (Ireland) - laboratories used for the analysis of the muscle samples and strength testing – Bio-medical Research (Ireland) – providing neuromuscular stimulators (Kneehab™) at no cost. No financial benefit or agreement has been received or made
Acronyms and abbreviations	BMI: body mass index NMES: neuromuscular electrical stimulation DCU: Dublin City University MRI: magnetic resonance imaging WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index SF-36: Short Form Health Survey-36 ROM: range of motion SCT: Stair Climb Test
Title	Effects of Kneehab™ 12-week Peri-operative Total Knee Arthroplasty (KneehabTKA)
Methods	Study design: randomized controlled trial Random sequence generation: not reported Allocation concealment: not reported Masking: single blind
Participants	Location: Liverpool, United Kingdom Target sample size (n): 200 participants Inclusion criteria: individuals who are scheduled for elective TKA surgery; individuals who are at least 18 years of age; individuals with a BMI <40; individuals who are walking independently with or without assistive devices; must be able and willing to complete all study assessments and to be followed for the full course of the study; must be able to read, write and follow instructions in English; must be able and willing to provide informed consent; must be willing and able to attend for preoperative assessment Exclusion criteria: individuals who have failed the preoperative assessment; individuals with a history of foot and/or ankle pathology; individuals with a history of tibial or femoral fractures; individuals with a history of underlying neurological conditions; individuals with physical conditions which would make them unable to perform study procedures; individuals with a total hip replacement; individuals undergoing revision TKA of the same operated leg; pregnant women or inadequate precautions to prevent pregnancy; diagnosis of a medical condition that would contraindicate treatment with the product, e.g. skin lesions at electrode site; individuals with an active implanted medical device (i.e. pacemaker, pump); individuals with a history of stroke; individuals with a history of neurological disorder that affects lower extremity function (stroke, peripheral neuropathy, Parkinson's disease, multiple sclerosis etc.); individuals with a diagnosis of inflammatory arthritis (including rheumatoid arthritis, gout or psoriatic arthritis); individuals with muscle disease (i.e. muscular dystrophy); visible skin injury or disease on their legs; principal investigator for this study, or member of study staff
Interventions	NMES group: Kneehab™ on the quadriceps of the affected leg, 20 minutes, twice per day, 5 days per week, over 12-week intervention (6 weeks before surgery, 6 weeks after surgery) Control Group: the Control Group will complete the standard physiotherapy care pre- and post-TKA surgery without NMES
Results	Primary outcomes: <ul style="list-style-type: none"> – Quadriceps activation – Quadriceps muscle strength (Torque): 3 dynamometer – Function: TUG and SCT Secondary outcomes: <ul style="list-style-type: none"> – Quality of life: SF-12 – Function and quality of life: WOMAC Timing of outcomes measurement: 6 weeks preoperative and 6, 12 and 52 weeks postoperative
Starting date	Main ID: NCT01096524 First received: March 24, 2010 Last updated: August 7, 2013 Status: not recruiting Estimated study completion date: completed

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Appendix 3. Ongoing studies characteristics

Contact information	Name: Dr. Alasdair Santini Address: not reported Telephone: not reported Contact: Bio-Medical Research, Ltd. Royal Liverpool and Broadgreen University Hospitals NHS Trust Affiliation: Bio-Medical Research, Ltd.; Royal Liverpool and Broadgreen University Hospitals NHS Trust
Acronyms and abbreviations	BMI: body mass index TKA: total knee arthroplasty CVA: cerebrovascular accident NMES: neuromuscular electrical stimulation TUG: Time Up and Go test SCT: Stair Climbing Test SF-12: Short Form Health Survey-12 WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
NCT01548040	
Title	Compare the Effects of a Standard Therapy Protocol With a 12-week Peri-Operative Program of Kneehab XP Neuromuscular Electrical Stimulation Compared to a Control Treatment in Patients Undergoing Total Knee Replacement
Methods	Study design: randomized controlled trial Random sequence generation: not reported Allocation concealment: not reported Masking: double-blind
Participants	Location: Greenville, South Carolina, United States Target sample size (n): 118 participants Inclusion criteria: individuals who are scheduled for TKA surgery with the Smith and Nephew Visionaire prosthesis and anterior surgical approach; individuals who are at least 40 years of age; individuals with a BMI <40kg/m ² ; individuals who are walking independently with or without assistive devices; individuals with a Short Performance Battery Score >7; must be able and willing to complete all study assessments and to be followed for the full course of the study; must be able to read, write and follow instructions in English; must be able and willing to provide informed consent; must be willing and able to attend the additional preoperative assessment Exclusion criteria: individuals with a history of foot and/or ankle pathology; individuals with a history of tibial or femoral fractures; individuals with a history of any underlying neurological conditions; individuals with physical conditions which would make them unable to perform study procedures; individuals with a total hip replacement; individuals undergoing revision TKA of the same operated leg; individuals who are pregnant; individuals diagnosed with a medical condition that would contraindicate treatment with the product, <i>e.g.</i> skin lesions at electrode site; individuals with an active implanted medical device (<i>i.e.</i> pacemaker, pump); individuals with a history of stroke; individuals with a history of neurological disorder that affects lower extremity function (stroke, peripheral neuropathy, Parkinson's disease, multiple sclerosis etc.); individuals with a diagnosis of inflammatory arthritis (rheumatoid arthritis, gout or psoriatic arthritis); individuals with muscle diseases (<i>i.e.</i> muscular dystrophy); individuals with visible skin injury or disease on their legs; individuals who have been committed to an institution by virtue of an order issued either by the courts or by an authority
Interventions	Kneehab™ group: NMES using Kneehab XP on the affected leg, 20 minutes, twice per day, 5 days a week. Subjects will begin use of the device at 6 weeks pre-operatively and continue through 6 weeks postoperatively Control Group (TENS): quadriceps TENS (at a minimal sensory input) using Kneehab XP on the affected leg, 20 minutes, twice per days, 5 days a week. Subjects will begin use of the device at 6 weeks preoperatively and continue through 6 weeks postoperatively
Outcomes	Primary outcomes: isometric strength test Secondary outcomes: pain; function; knee ROM; health economics outcomes Timing of outcomes measurement: 1 week pre-operatively, 3, 6, 12, 52 week post operatively
Starting date	Main ID: NCT01548040 Study first received: February 16, 2012 Last updated: March 21, 2012 Status: recruiting Estimated study completion date: incompleted
Contact information	Name: Brian MD Burnikel Address: not reported Telephone: 864-454-0904 E-mail: not reported Affiliation: Bio-Medical Research, Ltd.
Acronyms and abbreviations	TKA: total knee arthroplasty BMI: body mass index CVA: cerebrovascular accident NMES: neuromuscular electrical stimulation ROM: range of motion TENS: transcutaneous electrical nerve stimulation

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Appendix 3. Ongoing studies characteristics

NCT00224913	
Title	Electrical Stimulation After Total Knee Arthroplasty
Methods	Study design: randomized controlled trial Random sequence generation: not reported Allocation concealment: not reported Masking: single-blind
Participants	Location: Newark, Delaware, United States Target sample size (n): 200 Inclusion criteria: TKA for unilateral tricompartmental knee OA Exclusion criteria: insulin dependent diabetes; neurological conditions; other lower extremity orthopedic problems that affect function; BMI >40
Interventions	NMES group: patients will be asked to participate in functional and strength testing sessions, lasting about 1 hour and 30 minutes. MRI testing will last about 30 minutes per session and will be performed zero to 2 weeks before surgery, and 3 to 4 weeks, 10 to 12 weeks, and 1 year after surgery Control Group: patients will be asked to participate in functional and strength testing sessions, lasting about 1 hour and 30 minutes. MRI testing will last about 30 minutes per session and will be performed zero to 2 weeks before surgery, and 3 to 4 weeks, 10 to 12 weeks, and 1 year after surgery
Outcomes	Primary outcomes: function Secondary outcomes: not reported Timing of outcomes measurement: zero to 2 weeks before surgery, 3 to 4 weeks, 6 to 7 weeks, 10 to 12 weeks, 6 months, 1 year, and 2 years after surgery
Starting date	Main ID: NCT00224913 First received: September 21, 2005 Last updated: October 11, 2005 Last verified: October 2005. Status: unknown Estimated study completion date: concluded
Contact Information	Name: Lynn Snyder-Mackler Address: not reported Telephone: 302-831-3613 E-mail: smack@udel.edu Affiliation: Eunice Kennedy Shriver (NICHD)
Acronyms and abbreviations	TKA: total knee arthroplasty OA: osteoarthritis BMI: body mass index NMES: neuromuscular electrical stimulation MRI: magnetic resonance imaging NICHD: National Institute of Child Health and Human Development
NCT01844193	
Title	Early Postoperative Complex Rehab NMES Use for Total Knee Arthroplasty Patients
Methods	Study design: randomized controlled trial Random sequence generation: not reported Allocation concealment: not reported Masking: double-blind
Participants	Location: Indiana, United States Target sample size (n): 60 Inclusion criteria: patient is a candidate for unilateral primary TKA and has a primary diagnosis of osteoarthritis; patient is a male or non-pregnant female age 18 and older at time of surgery; patient has signed an IRB-approved, study-specific informed consent form; patient is willing and able to comply with the postoperative scheduled clinical evaluations and rehabilitation Exclusion criteria: patient has active infection within the affected knee joint; patient requires revision surgery of a previously implanted TKA; patient is morbidly obese, defined as having a BMI ≥ 36 ; patient has a neuromuscular or neurosensory deficiency, which limits the ability to evaluate the safety and efficacy of the intervention; patient has been diagnosed with a systemic disease or current life threatening illness and is not able to carry on normal activities of daily life (e.g. Paget's disease, renal osteodystrophy etc.); patient has a history of cardiac issues including myocardial infarction and/or has a pacemaker; patient is immunologically suppressed or receiving chronic steroids in excess of 5mg per day; patient has a recent history of substance dependency that may result in deviations from the evaluation schedule; patient is a prisoner; patient has indication for contralateral total knee arthroplasty within the evaluation window

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Appendix 3. Ongoing studies characteristics

NCT01844193	
Interventions	NMES group: participants in this arm will use a Compex® Rehab unit for neuromuscular electrical stimulation starting with postoperative at-home day 1 and continue using the unit twice a day, every day, until a 10-week follow-up is reached. The unit produces a 380-microsecond biphasic curve and utilizes a four phase process for the treatment ("Warm-up", "Work", "Relaxation", and "Recovery") for a total treatment time of 20 minutes and 5 seconds per session. All frequencies are delivered at the maximum subjective tolerable intensity. Participants will control this intensity and be asked to select a level that is tolerable although mildly uncomfortable; they will be instructed to increase this intensity as tolerated Control Group: not reported
Outcomes	Primary outcomes: change in quadriceps force Secondary outcomes: change in functional measurements of the quadriceps; change in pain medication requests; track narcotic/pain medication prescriptions for comparison between groups Timing of outcomes measurement: 2-week, 6-week, 10-week, and 1-year postoperative measurements
Starting date	Main ID: NCT01844193 First received: January 11, 2013 Last updated: April 26, 2013 Last verified: April 2013. Status: recruiting Estimated study completion date: incompleted
Contact information	Name: Frank R Kolisek Address: Greenwood, Indiana, United States, 46143 Telephone: 3178845200 Email: fkolisek@orthoindy.com Affiliation: Orthopaedic Research Foundation and DJO Incorporated
Acronyms and abbreviations	TKA: total knee arthroplasty IRB: Institutional Review Board BMI: body mass index NMES: neuromuscular electrical stimulation