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Neuromuscular electrical stimulation is effective in strengthening the quadriceps muscle after anterior cruciate ligament surgery

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Abstract
Purpose Reduced ability to contract the quadriceps muscles is often found immediately following anterior cruciate ligament (ACL) surgery. This can lead to muscle atrophy and decreased function. Application of neuromuscular electrical stimulation (NMES) may be a useful adjunct intervention to ameliorate these deficits following ACL surgery. The purpose of this review was to determine whether NMES in addition to standard physical therapy is superior to standard physical therapy alone in improving quadriceps strength or physical function following ACL surgery.

Methods A computer-assisted literature search was conducted utilizing PubMed, CINAHL, PEDro and Cochrane Library databases for randomized clinical trials where patients after ACL surgery received NMES with the outcome of muscle strength and/or physical function. Random effect models were used to pool summary estimates using standardized mean differences (SMD) for strength outcomes. Physical function outcomes were assessed qualitatively. Methodological quality was assessed from the Physiotherapy Evidence Database (PEDro)-score.

Results Eleven studies met our inclusion criteria; results from six of these were pooled in the meta-analysis showing a statistically significant short-term effect of NMES (4–12 weeks) after surgery compared to standard physical therapy [SMD = 0.73 (95% CI 0.29, 1.16)]. Physical function also improved significantly more in the NMES groups. PEDro scores ranged from 3/10 to 7/10 points.

Conclusion NMES in addition to standard physical therapy appears to significantly improve quadriceps strength and physical function in the early post-operative period compared to standard physical therapy alone.

Level of evidence I.

Keywords ACL · NMES · Physical therapy · Muscle strength · Quadriceps

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Introduction

The anterior cruciate ligament (ACL) is the most frequently injured ligament of the knee [1], and these injuries are amongst the most common in athletic populations with nearly 130,000 ACL reconstructions performed in USA alone in 2006 [27]. An ACL injury can be treated both conservatively and surgically with similar results but a lot of

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patients, especially the highly active ones, still choose surgical reconstruction of the ACL [29]. Criteria for determining when a patient is ready for return to sport typically include results from testing muscle strength or thigh circumference, general knee examination or single-leg hop tests [4, 40]. A recent systematic review shows only 65% return to their preinjury level of sport and 55% return to competitive level sport after ACL-surgery [2].

Reduced ability to make voluntary contractions of the quadriceps muscle is a common problem after knee injury even though there is no damage to the muscle or innervating nerve. This condition is often referred to as *arthrogenic muscle inhibition* [15, 18, 41, 44]. Muscle weakness after surgery or injury can partly be explained by atrophy of the muscle, but also this decreased ability to activate the muscle fibres available [15, 18]. The latter is suggested to be a protective, reflexive response to alter neural drive to the surrounding musculature after joint injury, hence precluding voluntary muscle work and normal function. However, the exact mechanisms eliciting and controlling quadriceps inhibition are unclear [15, 44].

Neuromuscular electrical stimulation (NMES) has been attempted in cases where voluntary muscle contractions are inhibited after injury or surgery because of its ability to induce action potentials in the motor nerves and overrule inhibition [15, 35, 44] thus making strength exercise possible. For clinicians working with ACL patients, NMES could possibly be a useful tool in rehabilitation when traditional exercises are limited by inhibition. The use of NMES in ACL rehabilitation to improve quadriceps strength and physical function has been subject to several randomized controlled trials (RCTs). Three prior systematic reviews on this topic [19, 20, 43] have concluded that NMES combined with exercise may be more effective in improving quadriceps strength than exercise alone [19, 20, 43], whereas its effect on functional performance and patient-oriented outcomes is inconclusive [20] and randomized controlled trials of better methodological quality, with adequate sample size and with at least 12 months of follow-up, are necessary [19]. Several RCTs on the subject have been published since the most recent included article in these reviews dated from the year 2003. Therefore, the purpose of this study was to synthesize current literature on the utilization of NMES to increase quadriceps strength and physical function compared to standard physical therapy following ACL surgery and determine treatment effectiveness for the outcome of strength with meta-analysis.

Materials and methods

This systematic review follows the guidelines of *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) [28]. A protocol was developed a priori to study initiation. This protocol was not published.

Data sources and search strategy

Literature searches were performed in PubMed, Embase, CINAHL and the Cochrane Library from the inception of each database to January 15 2016 for studies on ACL rehabilitation with NMES using Medical Subject Heading (MeSH) terms, free-text terms and the indexing vocabulary for each database. No limits were set for earliest publication date. See "Appendix" for entire search strategy. Bibliographies of previous systematic reviews [19, 20, 43] were also reviewed for any publications we might have missed. All citations were imported to one shared EndNote library for screening and inclusion.

Inclusion and exclusion criteria

To be included studies must be: (1) randomized controlled trials (RCTs), (2) the intervention group must have received NMES as an adjunct to standard physical therapy, (3) the control group must have received standard physical therapy without any adjunctive NMES intervention, (4) studies must consist of patients who have undergone ACL surgery of any kind, (5) adolescents and adults (aged 13 years or older), (6) primary outcome measurement of quadriceps or hamstrings muscle strength measured by isometric or isokinetic torque output, or physical performance measured by self-report or through standardized performance tests for muscle strength, stability or function of the lower limbs (7) and the studies must be published in English or Norwegian. Studies were excluded if they (1) were quasi-experimental or observational, (2) if NMES was not a primary intervention in the study or (3) if the study involved animal or cadaver testing.

Eligibility, screening and inclusion

Two trained investigators (AVH and LL) screened citations compared to the inclusions criteria. Abstracts were then screened against the inclusion/exclusion criteria for inclusion (AVH and MR). If the title or abstract was considered appropriate by one of the screeners, the article was moved to the full text review phase. Full texts were reviewed by two independent investigators (AVH and CS) against the inclusion/exclusion criteria. Disagreements by the investigators for inclusion were resolved by discussion or a third reviewer.

Data abstraction

Data from the included studies were abstracted by the first author (AVH) and verified by the fifth author (LL). Data elements for abstraction were decided on prior to data

abstraction and included; parameters of the NMES intervention (e.g., frequency, pulse width/duration, intensity and duty cycle), population characteristics (e.g., age, gender, type of ACL-surgery performed), intervention duration, training dosage, types of measurements, quality elements and test results. The authors were attempted to be contacted in the cases where data elements were not provided in the article.

Quality Assessment

To assess methodological study quality, the PEDro (Physiotherapy Evidence Database) quality assessment scale [33] was used. This scale utilizes a rating from 0 to 10 and is considered to be a valid measurement of methodological quality in RCTs [6] with an acceptable level of reliability [26]. All studies included in this review had previously been graded in the PEDro database by certified PEDro raters. These scores were utilized in our review (Table 1).

Data synthesis

Abstracted data elements were synthesized into tables. With the parameters synthesis, the stimulation time per week was calculated and in total based on on-time per duty cycle, length of each training session and amount of training sessions throughout the intervention. From these tables, both qualitative and quantitative analyses could be provided.

Quantitative synthesis (meta-analysis)

Quantitative syntheses were conducted when 3 or more studies were identified with the same outcome. DerSimonian and Laird random effect models with inverse variance weighting [8] were used to create pooled estimates since these models incorporate both within and between study heterogeneity into the pooled study confidence interval. Standardized mean differences (SMDs) were the measure of effect to account for variability in how the same outcome was measured by different studies. These SMDs represent the difference in post-intervention measurements that are standardized as a per cent of the mean value of the uninvolved lower extremity. If these means were not standardized to the uninvolved limb by the study authors, we standardized them by dividing by the mean score of the uninvolved limb of the same group, or solely by the uninvolved limb of the control group if NMES had been utilized on both limbs in the intervention group. A simple sensitivity analysis was conducted to determine potentially influential studies. This was conducted by removing each study and replacing and examining the overall pooled estimates from each of these models. We used Cochrane's Q with associated p value and I^2 to gauge pooled study heterogeneity with >75% to represent high heterogeneity, 50% to represent moderate and <25% to represent low heterogeneity [17]. Potential modifying covariates were abstracted from included studies in order to examine potential reasons for between study heterogeneity, these included: (1) stimulation time per week (<50 min/>50 min), (2) time of intervention start (during first postoperative week/after first postoperative week), (3) frequency of the current applied (≤50 Hz/>50 Hz), (4) individual items from the PEDro quality assessment scale, (5) restricted ROM of the knee during the intervention (No/Yes) and (6) type of graft (only hamstrings/only patellar tendon). Each of these covariates was examined in stratified analysis in attempt to explain heterogeneity.

Qualitative synthesis

When quantitative analyses were not conducted, a qualitative synthesis was provided individually for each outcome. For qualitative synthesis, more weight was placed on the results and our conclusions from higher quality studies. Potential reasons for why some studies show significant effect and others do not are described qualitatively by looking for differences in the populations, intervention protocols, control groups and compliance.

Results

The search identified 673 studies for potential inclusion of which 653 studies were excluded based on title and abstract screening. The remaining 20 studies went on to full-text review of which nine studies were excluded due to (1) non-randomized designs [5, 22, 30] (2) non-relevant outcome of interest [3, 11, 12], or (3) no control group receiving standard physical therapy [9, 10, 23]. Eleven studies [7, 13, 14, 16, 32, 34, 36–39, 42] qualified for this review with a kappa value of 0.79 indicating substantial agreement between authors (AV and CS) (online appendix), and six [7, 13, 32, 37, 39, 42] studies were included in the meta-analysis. Five studies were excluded from the meta-analysis with reasons: (1) not measuring isometric or isokinetic muscle strength [34], (2) not possible to standardize to uninvolved limb [36], (3) numbers not available, only graphs [16, 38], and (4) first follow-up too late compared to standard of 6 weeks [14]. The selection process is illustrated in Fig. 1, and a detailed description of the reasons for exclusion is available in the online appendix.

Table 1 Description of included studies' population, intervention, control groups, outcomes and study start and duration time

Authors	Population	Intervention	Control	Outcome	Time (start, duration)
Delitto et al.	19–44 years ACLrec Gender: N/A	N = 10 NMES + standard	N = 10 Standard	Isometric knee flex/ext	2nd/3rd PO-week 3 weeks
Feil et al.	18–55 years ACLrec Men and women	N = 45 NMES (PS) + standard N = 42 NMES (KH) + standard	N = 44 Standard	Isokinetic ext, single-legged jump, shuttle run, Lysholm score	3rd/4th PO-day 12 weeks
Fitzgerald et al.	29.2 ± 10.1(**I**) 31.9 ± 10.9(**C**) ACLrec Men and women	N = 21 NMES + standard	N = 22 Standard	Isometric ext, ADLS, milestones achieved	12.2 ± 6.7 PO-day 11 weeks
Hasegawa et al.	13–54 years ACLrec Men and women	N = 10 NMES + standard	N = 10 Standard	Isometric and isokinetic ext, Lysholm score	2nd PO-day 4 weeks
Paternostro-Sluga et al.	27.8 ± 7.1(**I**) 28.6 ± 11.3(**C**) ACLrec/ACLrep Men and women	N = 16 NMES + standard	N = 17 Standard	Isometric and isokinetic ext. Isokinetic flex.	3rd/5th PO-day 5.5 weeks
Ross et al.	27.1 ± 4.9(**I**) 28.4 ± 5.9(**C**) ACLrec Men and women	N = 10 NMES + CKCh exercise	N = 10 CKCh exercise	Unilateral Squat, Lateral step-up, Anterior Reach	7th PO-day 5 weeks
Sisk et al.	23.4 ± 7.5(**I**) 23.9 ± 9.2(**C**) ACLrec Men and women	N = 11 NMES + standard	N = 11 Standard	Isometric ext.	3rd/4th PO-day 6 weeks
Snyder-Mackler et al. (1991)	18–28 years ACLrec Men and women	N = 5 NMES + standard	N = 5 Standard	Gait analysis, isokinetic flex/ext.	3rd PO-week 4 weeks
Snyder-Mackler et al. (1995)	15–43 ACLrec Men and women	N = 31 HI-NMES + standard N = 25 LI-NMES + standard	N = 34 HL-exercise	Gait analysis, isometric ext.	1st PO-week 6 weeks
Taradaj et al.	17–29 years ACLrec Men *Soccer players*	N = 40 NMES + standard	N = 40 Standard	Isometric ext.	1st PO-week 4 weeks
Wigerstad-Lossing et al.	21–45 ACLrec Men and women	N = 13 NMES + standard	N = 10 Standard	Isometric ext.	2nd PO-day 6 weeks

NMES neuromuscular electrical stimulation, *ACLrec/rep* anterior cruciate ligament reconstructed/repaired. ***(I)***, intervention group, ***(C)*** control group, *Standard* standard rehabilitation, *Ext* extension, *Flex* flexion, *PO* PostOperative, *PS* Polystim, *KH* Kneehab, *IKDC* International Knee Documentation Committee (evaluation form), *ADLS* Activities of Daily Living Scale (self-report), *CKCh* closed kinetic chain, *HI* high intensity, *LI* low Intensity, *HL*high Level

Population characteristics

The populations across the studies were comparable in age. Most patients had undergone ACL reconstructive surgery; one study also included patients after ACL repair surgery [31]. All studies included both genders except Taradaj et al. [39] who included only male soccer players, whereas Delitto et al. [7] did not specify gender in the article. Isometric or isokinetic strength is the most common outcome measurement, while Feil et al. [13] also tested physical performance through *shuttle runs* and Ross [34] used a variety of tests for physical performance to evaluate the effect of the intervention.

Muscle strength

Six of the eleven studies were quantitatively summarized with the outcome of strength improvement in involved compared to uninvolved limb. These six were the only ones that had comparable outcome measures for a meta-analysis,

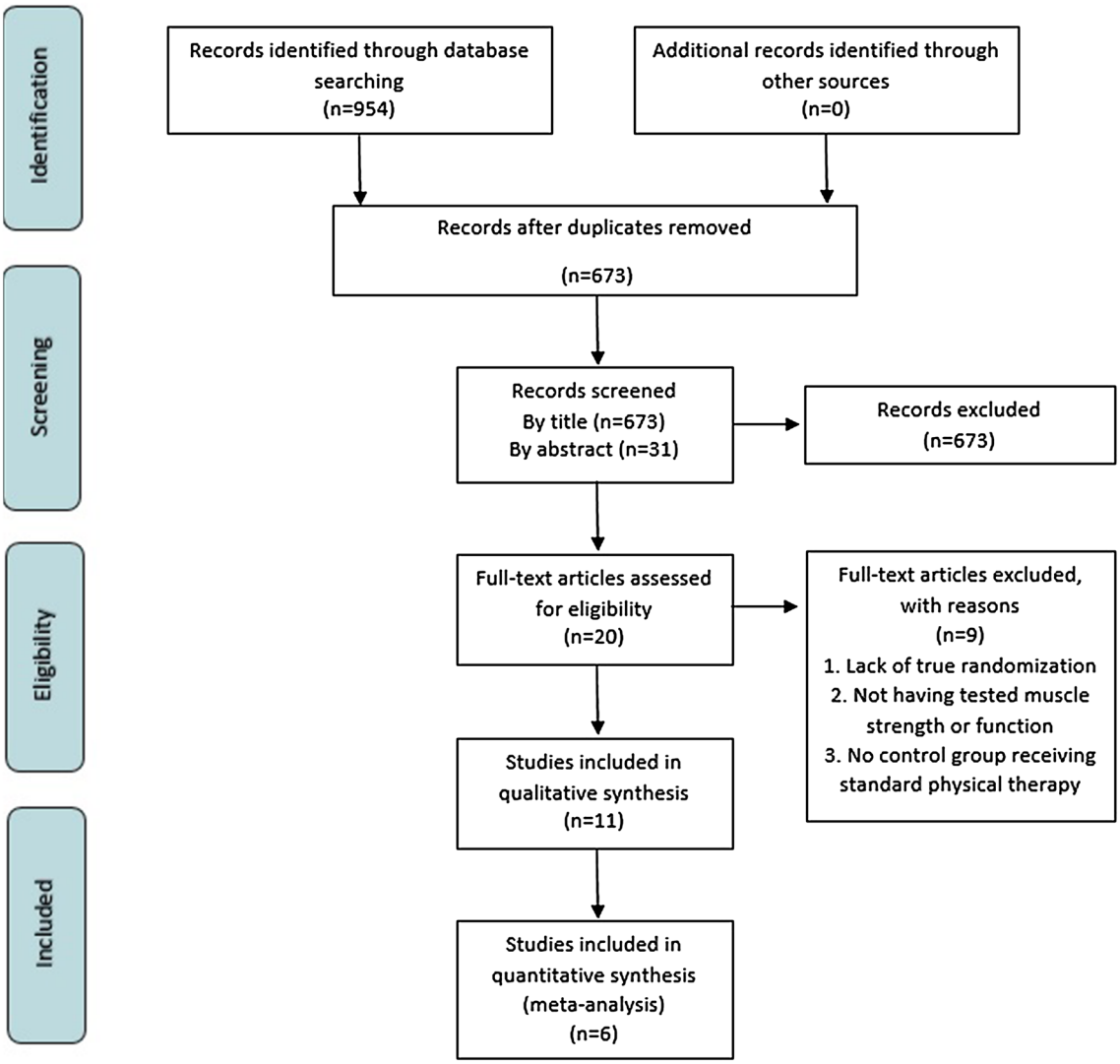

Fig. 1 PRISMA flow-chart

namely quadriceps strength in the involved limb as a % of strength in the uninvolved limb. Consistency in effects was noted across all six studies included in the meta-analysis with individual effect estimates ranging from SMD = 0.36 (−0.33, 1.5) to SMD = 2.20 (0.55, 3.84). Figure 2 illustrates the individual effect estimates along with an overall pooled estimate indicates a significant effect favouring the intervention arm [SMD = 0.73 (0.29, 1.16)] with significant heterogeneity ($I^2 = 55.4\%$, Q-p value = 0.047). Our sensitivity analysis revealed that single removal of each study resulted in a range of overall pooled estimates between 0.52 and 0.89 with removal of those studies with smaller samples sizes contributed to lower overall pooled estimates.

All included studies provided means for the intervention and control group standardized to the uninvolved limb or raw values for means of both limbs (Table 2). Taradaj et al. [39] performed the NMES intervention on both the involved and uninvolved limb and achieved strength progress in both, while the other studies only used NMES on the involved limb. The mean value for the uninvolved limbs of the control group was therefore used for comparison since that group had standard physical therapy. Only one intervention group (Kneehab group) of Feil et al. [13] was included in the meta-analysis to avoid skewing the weighting by using the same control group twice. The Kneehab group of this study was included since this effect estimate was more consistent with the

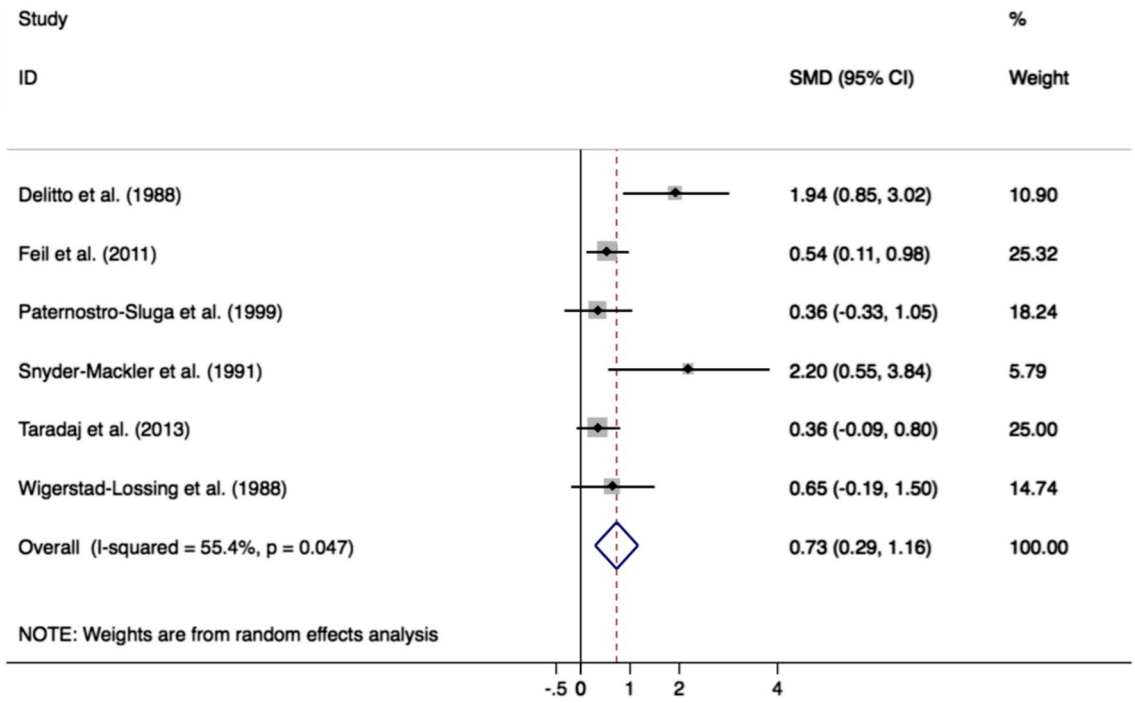

Fig. 2 Forest plot of studies included in meta-analysis of strength measurement

other published literature. A sensitivity analysis with and without the Polystim group (with the control group split to accommodate the three arm design) indicates the inclusion of this group to be a borderline outlier on the main effect analysis. Most studies performed measurements at several follow-ups; the measurement closest to 6 weeks postoperative has been used in Table 2 for comparison since that was most commonly used. A complete list of results can be found in the online appendix.

Moderator effects

Several covariates were examined as potential modifiers of the relationship between NMES and the outcome of strength. Time of intervention start was identified to be a significant modifier of the relationship between NMES and strength gains (Fig. 3). Delitto et al. [7] and Snyder-Mackler et al. [37] show the strongest effect of NMES [SMD = 1.94 (95% CI 0.85, 3.02) and SMD = 2.20 (95% CI 0.55, 3.84)], and they both started the intervention after the first postoperative week, while the four other studies started within the first week after surgery. Whereas when the estimates from Feil et al. [13], Paternostro-Sluga et al. [32], Taradaj et al. [39] and Wigerstad-Lossing et al. [42] were pooled it demonstrated a much weaker effect for NMES [SMD = 0.46 (95% CI 0.19, 0.73)]. This single moderator explained all of the heterogeneity with the main effects pooled estimate. See online appendix for forest plots of other modifying covariates.

Physical function

Feil et al. [13] and Hasegawa et al. [16] measured self-reported function using the Lysholm scale, a disease specific measure of knee function (Table 3). The only group showing improvement compared to the control group was the Kneehab group of Feil et al. [13] $p = 0.01$. Feil et al. [13] and Ross [34] tested physical performance through functional tests. Significantly better results were found in the Kneehab group in Feil et al. [13] $p < 0.001$ and Ross [34] found significantly better results for Lateral Step-up and Unilateral Squat $p < 0.05$ in the NMES group.

Parameters

Table 4 presents the details of the parameters used in the interventions. The on-time percentage and total on-time in minutes for the entire intervention and weekly was calculated from the ratio of on-time to off-time. These numbers vary greatly from Sisk et al. [36] who report a total of 840 min of active stimulation (on-time) per week in the NMES group to Fitzgerald et al. [14] where the NMES group received only

Table 2 Muscle strength measurement of hamstrings (flexion) and quadriceps (extension)

Authors	Outcome measurement (time after surgery)		Flexion		Diff./*p* value	Extension		Diff./*p* value
			NMES	Control		NMES	Control	
Delitto et al.	Isometric, % of ul	(5/6w)	94.1 (4.0)	70.0 (11.0)	24.1/<0.05	78.8 (14.0)	51.7 (14.0)	27.1/<0.05
Feil et al.	Isokinetic 90°/s, % of ul	(6w)		PS		65.7 (17.9)	73.1 (17.1)	−7.4/0.42
				KH		85.0 (26.1)		12.0/<0.001
	Isokinetic 180°/s, % of ul	(6w)		PS		65.6 (20.5)	69.4 (18.1)	−3.8/0.89
				KH		85.2 (24.2)		15.8/<0.001
Fitzgerald et al.	Isometric, % of ul	(12w)				75.9 (16.8)	67.0 (19.9)	8.9/<0.05
Hasegawa et al.	Isometric, % of baseline	(4w)				98.8		
	Not tested ul and numbers not available							
Paternostro-Sluga et al.	Isometric, % of ul	(6w)	62.4(23.2)	56.4 (21.0)	6.0/n.s.	69.1 (26.0)	60.7 (21.0)	8.4/n.s.
	Isokinetic, % of ul	(6w)				51.2 (21.6)	47.8 (18.1)	3.4/n.s.
Sisk et al.	Isometric, torque: weight **7w** ul not tested					0.73 (0.41)	0.70 (0.30)	0.03/n.s.
Snyder-Mackler et al. (1991)	Isokinetic 90°/s, % of ul	(8w)						
		Average	68.6 (5.1)	74.0 (23.3)	−5.4/> 0.05	70.1 (13.4)	46.7 (6.9)	23.4/<0.05
		Peak	78.9 (7.4)	71.2 (17.4)	7.7/> 0.05	68.7 (12.1)	43.5 (8.3)	25.2/<0.05
	Isokinetic 210°/s, % of ul	(8w)						
		Average	87.0(18.6)	75.8 (17.9)	11.2/> 0.05	68.9 (10.7)	43.7 (6.3)	25.2/<0.01
		Peak	84.1(10.7)	72.8 (25.0)	11.3/> 0.05	71.0 (9.6)	46.4 (6.3)	24.6/<0.01
Snyder-Mackler et al. (1995)	Isometric, % of ul	(4w)	Numbers not available. High intensity NMES reported superior to low intensity NMES and high level volitional exercise.					/<0.05
Taradaj et al.	Isometric compared to control ul[a]	(4–5w)				100.9 (82.3)	75.5 (58.1)	25.4/–
Wigerstad-Lossing et al.	Isometric, % of ul	(6w)				52.3 (18.76)	40.4 (17.48)	11.9/–

Method, time of measurement and results

ul uninvolved limb, *PS* Polystim, *KH* Kneehab, *n.s.* not significant, *W* weeks, *Diff* difference

[a] The control group received NMES-training on both injured and uninjured limb and increased strength in both. We therefore compare to the uninjured limb of the control group instead of the contralateral limb. SDs were obtained from Taradaj et al. [39] by e-mail contact, other authors did not respond to our request or we did not find correct contact information

3 min and 20 s of active stimulation per week. The intensity (amount of milliamperes) of the current used for stimulation was mostly reported as a qualitative perception of the maximum "tolerable" or "comfortable" intensity with a minimum requirement of achieving muscle contraction.

Quality assessment

PEDro scores range from 3/10 to 7/10 (Table 4 of online appendix). None of the studies blinded the therapists or the subjects, arguing that true blinding is not possible for this kind of treatment. PEDro quality assessment for blinding should therefore be interpreted with caution. Only two studies implemented "intention-to-treat" analysis [13, 14]. Four studies [13, 16, 32, 39] report that subjects were comparable at baseline.

Discussion

The principal finding of the present review was a significant effect of the intervention of NMES in addition to standard physical therapy treatment compared to the control groups who received standard physical therapy treatment alone after ACL surgery. Eleven studies met the inclusion criteria for the systematic review; six of these were pooled in the meta-analysis. This is the first systematic review with meta-analysis to examine the outcome of strength post-ACL surgery when comparing NMES in conjunction with standard

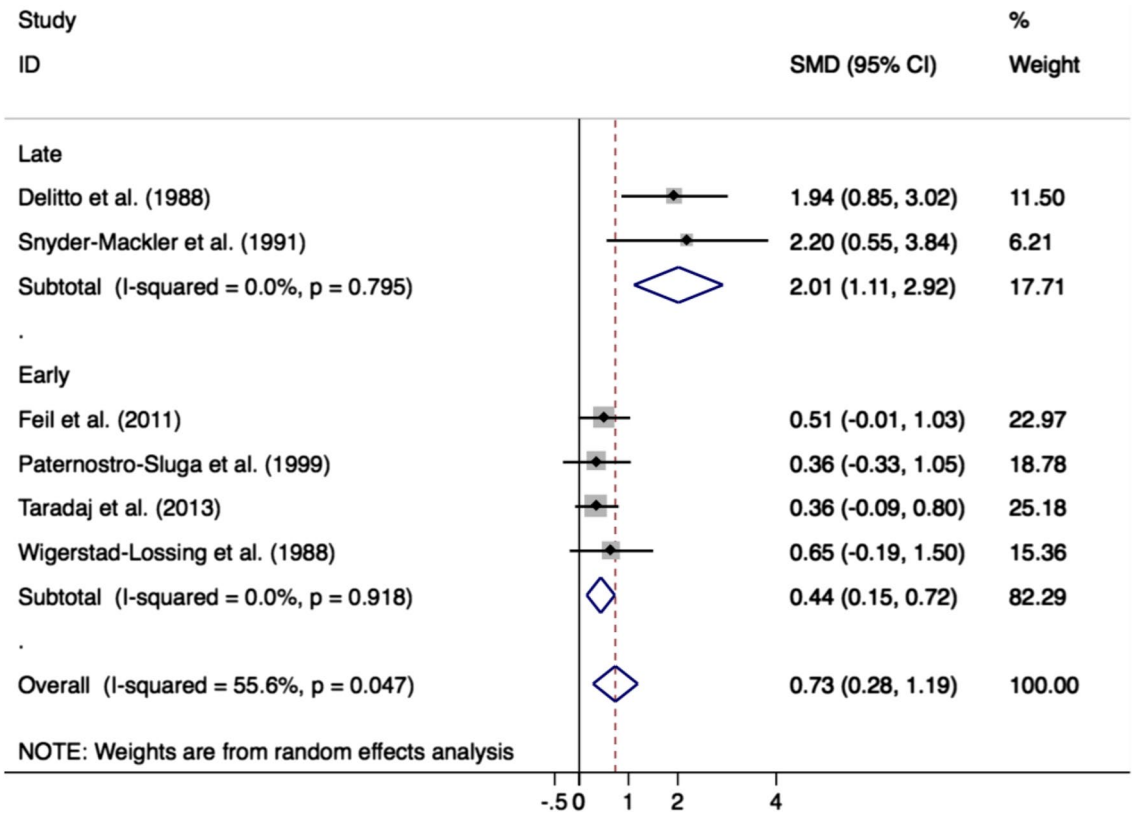

Fig. 3 Forest plot of studies included in meta-analysis of strength measurement, stratified by time of intervention start

Table 3 Self-reported and physical function

Authors	Outcome measurement (time after surgery)		NMES	Control	Diff/*p* value
Feil et al.	Lysholm	(6w)	PS: 87.45 (8.06)	88.21 (7.61)	−0.77/n.s.
			KH: 91.39 (4.87)		3.18/<0.01
		(12w)	PS: 94.03 (5.72)	95.35 (4.66)	−1.32/n.s.
			KH: 96.15 (3.46)		0.8/n.s.
		(24w)	PS: 97.45 (3.20)	98.31 (2.82)	−0.86/n.s.
			KH: 99.06 (2.19)		0.75/n.s.
Fitzgerald et al.	ADLS	(12w)	89.2 (8.9)	82.2 (10.4)	7.0/<0.05
Hasegawa et al.	Lysholm	(Preop.)	63.6 (15.5)	59.2 (24.7)	4.4/n.s.
		(24w)	96.4 (19.6)	95.2 (10.1)	1.2/n.s.
Feil et al.	Shuttle run, sec—baseline (Lower value = better result)	(6w)	PS: 3.21 (2.60)	2.04 (1.92)	1.17/0.14
			KH: 0.06 (3.11)		−1.98/<0.001
	Single-legged hop, cm	(6w)	PS:−34.99 (27.19)	−33.25 (27.87)	−1.74/0.90
			KH: −5.68 (41.21)		27.57/<0.001
Ross et al.	Unilateral squat[a]	(6w)	70.55 (18.46)	64.48 (15.36)	6.07/≤ 0.05
	Lateral step-up[b]	(6w)	17.65 (5.36)	14.35 (4.90)	3.3/≤ 0.05
	Anterior reach[c]	(6w)	58.75 (7.38)	58.30 (4.78)	0.45/> 0.05

w weeks, *Diff* difference, *n.s.* not significant, *PS* Polystim, *KH* Kneehab

[a] Degrees of knee flexion attained in weight bearing leg

[b] Max number of repetitions in 15 s

[c] Standing, reaching forward, measured in centimetres(cm)

Table 4 Parameters of neuromuscular electrical stimulation used by included studies

Authors	Hz	Pulse width (μs)	Duty cycle Sec on:off	On-time % of total	On-time total/per week (minutes)	Intensity (mA)
Delitto et al.	50	N/A	15:50	23	56/19	Max tolerable
Feil et al.	50	N/A	PS 10:20	33	1200/100	≤70
			KH 5:10	33		
Fitzgerald et al.	75	N/A	10:50	17	37/3	Max tolerable > tetanic
Hasegawa et al.	20	250	5:2	71	280/70	Max tolerable without discomfort, peak 74–107
Paternostro-Sluga et al.	30/50	N/A	5:15	25	308/56	Max tolerable > strong visible contraction
			10:50	17		
Ross et al.	50	200	15:35	30	189/38	Max tolerable > forceful contraction
Sisk et al.	40	300	10:30	25	5040/840	Max comfortable > palpable contraction
Snyder-Mackler et al. (1991)	75	400	15:50	23	45/11	Max tolerable
Snyder-Mackler et al. (1995)	75/55	300	HI 11:120	8	50/8	Max tolerable
			LI 15:50	23	414/69	Max tolerable >50
Taradaj et al.	50	200[a]	10:50	17	60/15	Strong, visible motion effects, 55–67
Wigerstad-Lossing et al.	30	300	6:10	38	274/46	Max tolerable, 65–100

Hz Hertz (frequency), *mA* milliampere, *μs* microseconds

[a] Pulse width was obtained from Taradaj et al. [39] by e-mail contact, other authors did not respond to our request or we did not find correct contact information

physical therapy. Two studies measuring physical function with standardized tests [13, 34] found significant results in the NMES group, but little difference between groups when it came to self-reported function. NMES protocols and devices utilized varied across studies.

All studies but two [31, 36] found a significant difference in favour of NMES and standard physical therapy compared to standard physical therapy alone and the result from this meta-analysis also favoured NMES, but only three [7, 13, 37] of the six studies showed differences between groups when assessing strength as a ratio of involved to uninvolved limb score. The changes from baseline to follow-up may be significant, but not necessarily compared to the uninvolved limb. All heterogeneity in the meta-analysis was explained by stratifying by time of intervention, favouring the studies where NMES was implemented after the first post-operative week. This finding differs with the conclusion and rationale of Hasegawa et al. [16] for starting the intervention as soon as possible after surgery to prevent muscle atrophy and maintain muscle strength.

Strength measurements after 6 weeks were our outcome for comparison due to its prevalence in the included studies. The clinical relevance of a 6-week strength measurement could be disputed since rehabilitation after ACL reconstruction usually lasts for six to twelve months [40] and the between group differences could be equivalent by then. Feil et al. [13] and Paternostro-Sluga et al. [32] were the only studies with long-term follow-up at 24 [13] and 52 [32] weeks (see online appendix for additional strength measurements). Feil et al. [13] reports significantly better results in the Kneehab group at 24 weeks compared to Polystim group and control, while Paternostro-Sluga et al. [32] found no statistical difference amongst groups. Taradaj et al. [39] reported 100% muscle strength achievement in the involved limb (compared to uninvolved limb of the control group) after only four to 5 weeks. Results such as this are not typically achieved.

Two studies [13, 34] performed standardized tests of physical performance and found better results in the NMES groups. Both Hasegawa et al. [16] and Feil et al. [13] reported greater strength gains in the intervention groups but only the Kneehab group in Feil et al. [13] scored higher on the Lysholm scale of self-reported function and only for the first follow-up. Feil et al. [13] describes the shuttle run they performed as a "walk/sprint test", therefore only utilizing this test 6 weeks post-surgery. Physical performance tests and self-reported function may provide a more valid presentation of the actual benefits NMES can provide in rehabilitation back to daily activities and sports than isometric or isokinetic strength measurements. Recent research suggests that the factors most strongly associated with return-to-sport status include self-reported knee function, episodes of knee instability and knee joint effusion [21]. While it is possible that these are factors that can be influenced by using NMES, most of the studies included in this review did not attempt to measure this.

The majority of the studies have described peak stimulation intensity as "maximum tolerable" or "maximum comfortable". Comfort tolerance likely varies greatly between subjects. Intensity dictates muscle fibre recruitment and work load [25]. The actual work load produced in these studies can also be variable when comparing 3–840 min of active stimulation time per week [14, 36].

This systematic review has several unique strengths including a comprehensive search with an independent dual investigator screening and inclusion process, the initial meta-analysis on strength measurements post-utilization of NMES after ACL surgery, and discussion regarding explanation of heterogeneous differences in the primary outcome of strength. However, our review is not without limitations. When three arm studies were identified, we chose one intervention group to be included. This was the case with Feil et al. [13] which compared two NMES devices (Polystim and Kneehab) to standard physical therapy. We chose the Kneehab group which showed significantly better results than both the Polystim group and the control group. Our sensitivity analysis indicates that including the Polystim group would be a borderline outlier on the main effect analysis. Another reason for this effect is that the authors report their source of funding to be a potential conflict of interest due to industry funding.

There are several limitations related to the quality of the included literature. No studies blinded the therapist or the subjects, but five studies [7, 13, 14, 32, 38] blinded assessors. Non-blinded study designs tend to show greater effects [26]. Only two studies [13, 14] had an "intention-to-treat" analysis which is an important measure to preserve the benefits of random assignment [24]. Four studies [13, 16, 32, 39] report that the subjects were comparable at baseline. The use of standardization in meta-analysis is sometime required to account for the differences in measures of the same outcome. This is the case with our meta-analysis where several studies measured strength using a different measure. Although the standardization provides a measure of comparison across studies, it does limit the clinical interpretation.

Conclusion

The addition of NMES to standard physical therapy appears to significantly increase quadriceps muscle strength compared to conventional physical therapy alone. Early strength gains can be beneficial to avoid quadriceps muscle inhibition and atrophy, providing the rehabilitation subject with the most effective course of rehabilitation and return to sports. Improvements in self-reported physical function were also found; however, NMES did not influence self-reported function beyond 6-week follow-up. Studies with longer follow-ups are required to determine whether NMES gives any advantages in the long term.

Compliance with ethical standards

Conflict of interest The authors of this article have no conflicts of interest on the matter presented.

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Ethical approval No ethical approval has been necessary since sensitive information has not been provided or utilized in this review.

Appendix: Search strategies

See Tables 5, 6, 7 and 8.

Table 5 Search strategy PubMed

PubMed
("anterior cruciate ligament reconstruction"[MeSH Terms] OR "anterior cruciate ligament reconstruction"[tiab] OR "Anterior Cruciate Ligament/surgery"[Mesh] OR "Anterior Cruciate Ligament surgery"[tiab] OR (ACL[tiab] AND "reconstructive surgical procedures"[MeSH Terms]) OR " ACL reconstruction"[tiab] OR "quadriceps muscle"[MeSH Terms] OR "quadriceps"[tiab]) AND ("electric stimulation"[MeSH Terms] OR Electric Stimulation Therapy[mesh] OR "neuromuscular electrical stimulation"[tiab] OR NMES[tiab]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case–control studies"[MeSH Terms] OR "case–control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])
Returned **558** articles

Table 6 Search strategy Embase

Embase		
No.	Query	Results
#1	'anterior cruciate ligament'/exp OR 'anterior cruciate ligament' OR 'anterior cruciate ligament reconstruction'/exp OR 'anterior cruciate ligament reconstruction' OR 'anterior cruciate ligament surgery' OR 'acl reconstruction'	18,572
#2	'anterior cruciate ligament'/exp OR 'anterior cruciate ligament' OR 'acl'	22,967
#3	'surgery'/exp OR 'surgery' OR 'reconstructive surgery'/exp OR 'reconstructive surgery'	5,331,275
#4	#2 AND #3	15,930
#5	'quadriceps'/exp OR 'quadriceps' OR 'quadriceps femoris muscle'/exp OR 'quadriceps femoris muscle'	18,462
#6	#1 OR #4 OR #5	36,487
#7	'electric stimulation'/exp OR 'electric stimulation' OR 'electric stimulation therapy'/exp OR 'electric stimulation therapy' OR 'electrostimulation'/exp OR 'electrostimulation' OR 'electrostimulation therapy'/exp OR 'electrostimulation therapy' OR 'neuromuscular electrical stimulation'/exp OR 'neuromuscular electrical stimulation' OR 'nmes'	270,113
#8	#6 AND #7	1722
#9	#6 AND #7 AND([Cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND ([article]/lim OR [article in press]/lim) AND ([English]/lim OR [norwegian]/lim) AND [humans]/lim AND ([embase]/lim OR [embase classic]/lim)	**139**

Table 7 Search strategy CINAHL

CINAHL		
No.	Query	Results
S1	(MH "Anterior Cruciate Ligament Reconstruction") OR "anterior cruciate ligament reconstruction" OR (MH "Anterior Cruciate Ligament/SU")	3876
S2	"Anterior Cruciate Ligament Surgery"	1419
S3	(MH "Surgery, Reconstructive+") AND "ACL"	904
S4	"ACL reconstruction"	1263
S5	"quadriceps" OR (MH "Quadriceps Muscles+")	5147
S6	S1 OR S2 OR S3 OR S4 OR S5	9180
S7	(MH "Electric Stimulation+") OR (MH "Electrical Stimulation, Neuromuscular")	12706
S8	"Electric Stimulation Therapy" OR "NMES"S9	289
S9	S7 OR S8	12792
S10	S6 AND S9	466
S11	S6 AND S9 Limiters—English Language, Randomized Controlled Trials	**44**

Table 8 Search strategy Cochrane

Cochrane		
No.	Query	Results
#1	"anterior cruciate ligament reconstruction" or "Anterior Cruciate Ligament surgery" or "ACL reconstruction" or "quadriceps"	2876
#2	"electric stimulation" or "Electric Stimulation Therapy" or "neuromuscular electrical stimulation" or NMES	3710
#3	#1 and #2	**232**

References

1. Agel J, Arendt EA, Bershadsky B (2005) Anterior cruciate ligament injury in National Collegiate Athletic Association basketball and soccer a 13-year review. Am J Sports Med 33(4):524–531
2. Ardern CL, Taylor NF, Feller JA, Webster KE (2014) Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors. Br J Sports Med 33(21):1543–1552
3. Arvidsson I, Arvidsson H, Eriksson E, Jansson E (1986) Prevention of quadriceps wasting after immobilization: an evaluation of the effect of electrical stimulation. Orthopedics 9(11):1519–1528
4. Barber-Westin SD, Noyes FR (2011) Factors used to determine return to unrestricted sports activities after anterior cruciate ligament reconstruction. Arthroscopy 27(12):1697–1705
5. Currier DP, Ray JM, Nyland J, Rooney JG, Noteboom JT, Kellogg R (1993) Effects of electrical and electromagnetic stimulation after anterior cruciate ligament reconstruction. JOSPT J Orthop Sports Phys Ther 17(4):177–184
6. de Morton NA (2009) The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother 55(2):129–133
7. Delitto A, Rose SJ, McKowen JM, Lehman RC, Thomas JA, Shively RA (1988) Electrical stimulation versus voluntary exercise in strengthening thigh musculature after anterior cruciate ligament surgery. Phys Ther 68(5):660–663
8. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
9. Draper V, Ballard L (1991) Electrical stimulation versus electromyographic biofeedback in the recovery of quadriceps femoris muscle function following anterior cruciate ligament surgery. Phys Ther 71(6):455–461
10. Draper V, Lyle L, Seymour T (1997) From the Field-EMG biofeedback versus electrical stimulation in the recovery of quadriceps surface EMG. Clin Kinesiol 51:28–32
11. Ediz L, Ceylan MF, Turktas U, Yanmis I, Hiz O (2012) A randomized controlled trial of electrostimulation effects on effussion, swelling and pain recovery after anterior cruciate ligament reconstruction: a pilot study. Clin Rehabil 26(5):413–422
12. Eriksson E, Häggmark T (1979) Comparison of isometric muscle training and electrical stimulation supplementing isometric muscle training in the recovery after major knee ligament surgery: a preliminary report. Am J Sports Med 7(3):169–171
13. Feil S, Newell J, Minogue C, Paessler HH (2011) The effectiveness of supplementing a standard rehabilitation program with

superimposed neuromuscular electrical stimulation after anterior cruciate ligament reconstruction: a prospective, randomized, single-blind study. Am J Sports Med 39(6):1238–1247
14. Fitzgerald GK, Piva SR, Irrgang JJ (2003) A modified neuromuscular electrical stimulation protocol for quadriceps strength training following anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther 33(9):492–501
15. Hart JM, Pietrosimone B, Hertel J, Ingersoll CD (2010) Quadriceps activation following knee injuries: a systematic review. J Athl Train 45(1):87–97
16. Hasegawa S, Kobayashi M, Arai R, Tamaki A, Nakamura T, Moritani T (2011) Effect of early implementation of electrical muscle stimulation to prevent muscle atrophy and weakness in patients after anterior cruciate ligament reconstruction. J Electromyogr Kinesiol 21(4):622–630
17. Higgins J, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558
18. Hopkins JT, Ingersoll CD (2000) Arthrogenic muscle inhibition: a limiting factor in joint rehabilitation. J Sport Rehabil 9(2):135–159
19. Imoto AM, Peccin S, Almeida GJM, Saconato H, Atallah ÁN (2011) Effectiveness of electrical stimulation on rehabilitation after ligament and meniscal injuries: a systematic review. Sao Paulo Med J 129(6):414–423
20. Kim K-M, Croy T, Hertel J, Saliba S (2010) Effects of neuromuscular electrical stimulation after anterior cruciate ligament reconstruction on quadriceps strength, function, and patient-oriented outcomes: a systematic review. J Orthop Sports Phys Ther 40(7):383–391
21. Lentz TA, Zeppieri G Jr, Tillman SM, Indelicato PA, Moser MW, George SZ, Chmielewski TL (2012) Return to preinjury sports participation following anterior cruciate ligament reconstruction: contributions of demographic, knee impairment, and self-report measures. J Orthop Sports Phys Ther 42(11):893–901
22. Lepley LK, Wojtys EM, Palmieri-Smith RM (2015) Combination of eccentric exercise and neuromuscular electrical stimulation to improve quadriceps function post-ACL reconstruction. Knee 22(3):270–277
23. Lieber RL, Silva PD, Daniel DM (1996) Equal effectiveness of electrical and volitional strength training for quadriceps femoris muscles after anterior cruciate ligament surgery. J Orthop Res 14(1):131–138
24. Littell JH, Corcoran J, Pillai V (2008) Systematic reviews and meta-analysis. Oxford University Press, Oxford, pp 60–71
25. Low J, Reen A (2000) Electrotherapy explained: principles and practice. Butterworth-Heinemann, Oxford, pp 70–76
26. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M (2003) Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 83(8):713–721
27. Mall NA, Chalmers PN, Moric M, Tanaka MJ, Cole BJ, Bach BR Jr, Paletta GA Jr (2014) Incidence and trends of anterior cruciate ligament reconstruction in the United States. Am J Sports Med 42(10):2363–2370
28. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Stewart LA (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Sys Rev 4(1):1
29. Moksnes H, Risberg MA (2009) Performance-based functional evaluation of non-operative and operative treatment after anterior cruciate ligament injury. Scand J Med Sci Sports 19(3):345–355
30. Morrissey MC, Brewster CE, Shields CL Jr, Brown M (1985) The effects of electrical stimulation on the quadriceps during postoperative knee immobilization. Am J Sports Med 13(1):40–45
31. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE (2014) Incidence of second ACL injuries 2 years after primary ACL reconstruction and return to sport. Am J Sports Med 42(7):1567–1573
32. Paternostro-Sluga T, Fialka C, Alacamliogliu Y, Saradeth T, Fialka-Moser V (1999) Neuromuscular electrical stimulation after anterior cruciate ligament surgery. Clin Orthop Relat Res 368:166–175
33. PEDro. PEDro, Physiotherapy Evidence Database. 2016 04.04.2016 [cited 2016 04.22.2016]; http://www.pedro.org.au/english/faq/#question_five
34. Ross M (2000) The effect of neuromuscular electrical stimulation during closed kinetic chain exercise on lower extremity performance following anterior cruciate ligament reconstruction. Res Sports Med 9(4):239–251
35. Saka T (2014) Principles of postoperative anterior cruciate ligament rehabilitation. World J Orthop 5(4):450–459
36. Sisk TD, Stralka SW, Deering MB, Griffin JW (1987) Effect of electrical stimulation on quadriceps strength after reconstructive surgery of the anterior cruciate ligament. Am J Sports Med 15(3):215–220
37. Snyder-Mackler L, Ladin Z, Schepsis AA, Young JC (1991) Electrical stimulation of the thigh muscles after reconstruction of the anterior cruciate ligament. Effects of electrically elicited contraction of the quadriceps femoris and hamstring muscles on gait and on strength of the thigh muscles. J Bone Joint Surg Am 73(7):1025–1036
38. Snyder-Mackler L, Delitto A, Bailey SL, Stralka SW (1995) Strength of the quadriceps femoris muscle and functional recovery after reconstruction of the anterior cruciate ligament. A prospective, randomized clinical trial of electrical stimulation. J Bone Joint Surg Am 77(8):1166–1173
39. Taradaj J, Halski T, Kucharzewski M, Walewicz K, Smykla A, Ozon M, Pasternok M (2013) The effect of neuromuscular electrical stimulation on quadriceps strength and knee function in professional soccer players: return to sport after ACL reconstruction. Biomed Res Int 2013:802534. doi:10.1155/2013/802534
40. Thomeé R, Kvist J (2015) Structured Rehabilitation Model with Clinical Outcomes After Anterior Cruciate Ligament Reconstruction. In: Doral MN, Karlsson J (eds) Sports injuries. Springer, Berlin, pp 1439–1465
41. Urbach D, Nebelung W, Weiler HT, Awiszus F (1999) Bilateral deficit of voluntary quadriceps muscle activation after unilateral ACL tear. Med Sci Sports Exerc 31(12):1691–1696
42. Wigerstad-Lossing I, Grimby G, Jonsson T, Morelli B, Peterson L, Renström P (1988) Effects of electrical muscle stimulation combined with voluntary contractions after knee ligament surgery. Med Sci Sports Exerc 20(1):93–98
43. Wright RW, Preston E, Fleming B, Amendola A, Andrish JT, Bergfeld JA, Dunn WR, Kaeding C, Kuhn JE, Marx RG, McCarty EC, Parker RC, Spindler KP, Wolcott M, Wolf BR, Williams GN (2008) A systematic review of anterior cruciate ligament reconstruction rehabilitation: part II: open versus closed kinetic chain exercises, neuromuscular electrical stimulation, accelerated rehabilitation, and miscellaneous topics. J Knee Surg 21(3):225–234
44. Young A (1993) Current issues in arthrogenous inhibition. Ann Rheum Dis 52(11):829–834