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Cross-education does not improve early and late-phase rehabilitation outcomes after ACL reconstruction: a randomized controlled clinical trial

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Abstract

Purpose Limited evidence suggests that cross-education affords clinical benefits in the initial 8 weeks after anterior cruciate ligament (ACL) reconstruction, but it is unknown if such cross-education effects are reproducible and still present in later phases of rehabilitation. We examined whether cross-education, as an adjuvant to standard therapy, would accelerate the rehabilitation up to 26 weeks after ACL reconstruction by attenuating quadriceps weakness.

Methods ACL-reconstructed patients were randomized into experimental ($n=22$) and control groups ($n=21$). Both groups received standard care after ACL reconstruction. In addition, the experimental group strength trained the quadriceps of the non-operated leg during weeks 1–12 after surgery (i.e., cross-education). Self-reported knee function was assessed with the Hughston Clinic Knee score as the primary outcome. Secondary outcomes were maximal quadriceps and hamstring strength and single leg hop distance. All outcomes were measured 29 ± 23 days prior to surgery, as a reference, and at 5-week, 12-week, and 26-week post-surgery.

Results Both groups scored 12% worse on self-reported knee function 5-week post-surgery (95% CI 7–17) and showed 15% improvement 26-week post-surgery (95% CI − 20 to − 10). No cross-education effect was found. Interestingly, males scored 8–10% worse than females at each time point post-surgery. None of 33 secondary outcomes showed a cross-education effect. At 26-week post-surgery, both legs improved maximal quadriceps (5–14%) and hamstring strength (7–18%), and the non-injured leg improved 2% in hop distance. The ACL recovery was not affected by limb dominance and age.

Conclusion 26 weeks of standard care improved self-reported knee function and maximal leg strength relative to pre-surgery and adding cross-education did not further accelerate ACL recovery.

Level of evidence I.

Clinical Trial Registry name and registration This randomized controlled clinical trial is registered at the Dutch trial register (http://www.trialregister.nl) under NTR4395.

Keywords Anterior cruciate ligament reconstruction · Hughston Clinic Knee score · Limb symmetry index · Maximal voluntary force · Resistance training

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00167-018-5116-y) contains supplementary material, which is available to authorized users.

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Introduction

Anterior cruciate ligament (ACL) reconstruction restores knee laxity in the sagittal plane but quadriceps weakness persists [25]. This weakness is associated with greater limb asymmetries in hop distance and poor self-reported function [32], and seems greater for patellar tendon than hamstring tendon autografts [21]. Some [6, 18], but not all studies [42] report that quadriceps weakness is present also in the contralateral non-injured leg up to 24 months after ACL surgery. Hence, training both legs after an ACL surgery might improve the outcome of rehabilitation [25].

Rehabilitation after ACL reconstruction has been recommended to consist of strength and neuromuscular training to minimize the risk of a second ACL injury [8, 38]. Strengthening the quadriceps in the early phase of ACL rehabilitation is, however, difficult due to knee pain, effusion, and concerns about graft elongation when loading the quadriceps [38]. Therefore, it is not surprising that quadriceps' strength in the reconstructed leg decreases rapidly in the first months after surgery [14]. Cross-education, which is the increase in motor output in a limb muscle after resistance training of the homologous muscle in the contralateral limb [5], might, as an adjuvant to standard therapy, minimize strength loss in the early phase after ACL reconstruction [26] and also reduce weakness in the non-operated leg [6, 18]. Cross-education is also relevant to ACL rehabilitation, because it acts through neural pathways that are involved in the strength loss [31]. Evidence for a strength-sparing effect produced by cross-education comes from immobilization studies in which strength training of the free limb attenuated strength loss and atrophy in healthy adults' immobilized limb [3, 28]. Neural mechanisms are likely to mediate such a strength-maintenance effect [28].

Cross-education studies in patients with unilateral orthopedic injuries are scant [19, 26, 27], but they all confirm that cross-education improves rehabilitation outcomes when added to standard care. To illustrate, ACL-reconstructed patients showed less quadriceps weakness [26] and a better self-reported function [27] following additional eccentric strength training with the non-injured leg in the initial 8 weeks after surgery. However, it is unclear if such cross-education effects are reproducible and if the early benefits persist through the later phases of rehabilitation.

The purpose of the present study was to examine if adding cross-education to standard care in the first 12 weeks after ACL reconstruction could accelerate the recovery in the early and late phase of ACL rehabilitation. The ACL patients subjected to additional strength training of the non-injured leg were expected to show accelerated recovery in self-reported knee function, maximal quadriceps' strength, and single leg hop distance at 5 weeks, 12 weeks, and 26 weeks after surgery. The recovery of maximal hamstring strength would not be accelerated as the cross-education intervention was designed to target quadriceps' weakness.

Materials and methods

This study was a randomized controlled trial where patients were tested 29 ± 23 days prior to ACL surgery and at 5-week, 12-week, and 26-week post-surgery. Patients were individually randomized to one of two parallel groups in a 1:1 ratio, to receive either the standard care or standard care plus cross-education intervention. An independent physiotherapist allocated the patients to one of two treatment groups according to a computer generated randomization list prepared by an investigator who was not involved in data collection. Group allocation was completed after surgery but before the start of the rehabilitation program. Except for the physiotherapists administering the treatment, orthopedic surgeons and data collectors were blinded to patients' group assignment.

Participants

Patients awaiting ACL reconstruction were recruited for 2 years from the Martini Hospital in Groningen, The Netherlands, under the direction of two orthopedic surgeons. The patients who were scheduled for ACL surgery and met the inclusion criteria were invited to take part in the study. Inclusion criteria were: age between 18 years and 60 years, unilateral ACL tear with/without partial meniscal resection, time between ACL injury and testing < 2 years, autograft, allograft or artificial graft of any source, and minimal one supervised rehabilitation session per week. Patient exclusion criteria were: previous ACL reconstruction, history of a lower limb injury that required surgery, pregnancy, and current or prior neurological conditions. The pre and post-injury physical activity level was determined using the Tegner activity score [34]. Leg dominance was determined using the Waterloo Footedness questionnaire [9].

Intervention

The control and experimental group performed the standard rehabilitation protocol as described in Table 1. In addition, the experimental group performed quadriceps' strengthening exercises with the non-injured leg (i.e., cross-education training). These exercises consisted of three sets at an 8–12 repetition maximum on the leg press and leg extension machine with a 1- to 2-min rest period. The cross-education training aimed to

Table 1 Rehabilitation program after ACL reconstruction

Phase	Weeks	Content
Phase 1: active mobilization	1–4	Mobilization, focus on passive extension (first 2 weeks) Reducing inflammation Quadriceps strength 3 × 15 reps per leg (leg press, leg extension) Straight leg raises 3 × 10 reps per leg
Phase 2: basic strength	4–12	Minimizing inflammation Quadriceps' strength 3 × 15 reps per leg (leg press; leg extension) Hamstring strength 3 × 15 reps per leg (leg curl) Squats 3 × 15 reps Good mornings 3 × 15 reps Straight leg raises 3 × 10 reps per leg Step ups 3 × 10 reps per leg Balance and core stability exercises
Phase 3: maximal strength	12–24	Strength exercises as above (4 × 10 reps or pyramid strength 14/12/10/8 reps, progression after a few weeks to 10/8/6/4 reps) Balance and core stability exercises Start running, with a minimal change in direction/pivoting Basic two legged jumping tasks
Phase 4: power and jumping	24–36	Power training, working on strength deficits Progress running, directional changes/pivoting Progress from two legged to one legged jumping tasks

maximize hypertrophy and was performed in week 1–12 after ACL reconstruction [2]. The resistance for the cross-education training increased ~8% over time. The physiotherapists ensured that the patients received an adequate training stimulus by gradually increasing the resistance at which patients trained. Every patient trained twice a week supervised by a physiotherapist. Physiotherapist kept a training log for every patients, but compliance to the home exercise program was not monitored.

Flow of patients through the study

Online Resource 1 shows the flow of patients through the study. From December 2013 to February 2016, 124 patients were assessed for eligibility. Of these, 12 (10%) did not met the inclusion criteria and 54 (44%) declined to participate. The remaining 58 patients (47%) underwent pre-surgery testing. One patient did not undergo surgery and two patients were excluded, because the time between injury and surgery became more than 2 years. Fifty-five patients were randomized after surgery and started the intervention. Four patients deviated from the protocol as they received the control group treatment, while they were allocated to the experimental group. Of these, 43 (78%) were included in the final analysis. Table 2 shows the group characteristics of the patients that were included in the final analysis.

Outcome measures

Primary outcome

The primary outcome was self-reported knee function assessed with the Hughston Clinic Knee (HCK) questionnaire [10]. The HCK questionnaire rates subjective knee complaints through answers marked on a visual analogue scale (0–10) to 28 questions [10]. These questions comprise symptoms of the knee, functioning in sports, and functioning in activities of daily living. The score on each question was converted to a percentage and the mean percentage, calculated over 28 questions, was used in the analysis. A score of 0% means no knee complaints. The HCK questionnaire is reliable, valid, and sensitive to changes over time in ACL patients recovering from reconstructive surgery [10, 15]. The HCK questionnaire is not as often utilized in ACL research, but, for patients, it is an easier questionnaire to complete and understand relative to other questionnaires [10]. Thereby, scores on the HCK questionnaire correlate highly with scores on the Cincinnati Knee questionnaire ($r = 0.91$) and Lysholm Knee questionnaire ($r = 0.88$), questionnaires that are often used in ACL research [15].

Table 2 Mean (SD) baseline characteristics of the participants

	Experimental group ($n=22$)	Control group ($n=21$)	p value
Age (years)	28 (9)	28 (10)	(n.s.)
Sex			0.022*
Male	16	8	
Female	6	13	
Mass (kg)	82 (13)	74 (10)	0.029*
Height (cm)	182 (8)	175 (6)	0.002*
BMI (kg/m^2)	25 (3)	24 (3)	(n.s.)
Leg dominance			(n.s.)
Left	3	3	
Right	19	18	
Operated leg			(n.s.)
Dominant	12	15	
Non-dominant	10	6	
Graft type			(n.s.)
Hamstring tendon	18	19	
Bone-patellar tendon-bone	3	2	
Artificial	1	0	
Tegner score			
Pre-injury	8 (2)	7 (2)	(n.s.)
Post-injury	4 (1)	4 (1)	(n.s.)
Number of training sessions	44 (11)	50 (12)	(n.s.)
Time between injury and pre-surgery testing (days)	189 (138)	160 (95)	(n.s.)
Time between pre-surgery testing and surgery (days)	28 (28)	30 (17)	(n.s.)

*Group difference ($p<0.05$)

Secondary outcomes

The secondary outcomes were maximal quadriceps' torque, maximal hamstring torque, and single leg hop distance (see explanation below). The secondary outcomes were assessed in each leg in one of three random orders, with the starting leg being also randomly selected, and the randomization carried forward to subsequent testing sessions.

Maximal quadriceps and hamstring torque

Isometric and dynamic (eccentric 60°/s and concentric 60°/s, 120°/s, 180°/s) quadriceps and hamstring maximal voluntary contractions (MVCs) were measured on an isokinetic dynamometer (Biodex Medical Systems, Shirley, NY, USA) using an established protocol [42]. Strength testing was preceded by a 5-min warm-up on a bicycle ergometer. Every contraction condition started with two familiarization trials at 50% of the patients' estimated MVC followed by three maximal contractions to obtain the isometric and eccentric MVCs and six maximal contractions to obtain the concentric MVCs [42]. Patients were randomly subjected to one of three different contraction orders. There was a 1-min break between repetitions and contraction conditions. The peak torque, normalized to body weight, was used in the statistical analysis. The test–retest reliability of these measurements in ACL-reconstructed patients is good-to-excellent [37].

Single leg hop distance

The hop distance was examined in a subsample of patients as not all patients were cleared by their physiotherapist to perform this test (experimental group: $n=18$; control group: $n=16$). Patients performed the single leg hop test for distance as published previously [42], with excellent test–retest reliability [1]. Two practice trials were followed by two scored single leg hops. The hop distance was measured from the toe at push-off to the heel where landed. The maximal hop distance of the two trials was used in the analysis.

In accordance with the Declaration of Helsinki, all patients provided written informed consent to the experimental procedures, which were approved by the medical ethics committee of the University Medical Center Groningen (ID 2012.362). This randomized controlled clinical trial is registered at trialregister.nl identifier: NTR4395.

Statistical analysis

Data in the text and figures are presented as mean ± SD. A modified intention-to-treat analysis was performed that included all patients who were randomized for treatment and attended at least two test sessions. Normality was checked for each variable. Group characteristics of the two groups were compared with a one-way ANOVA when measured on a ratio scale and with a Kruskal–Wallis or Chi-square test when measured on, respectively, an ordinal or nominal scale.

The primary and secondary outcome measures were analysed using multilevel analysis (SPSS version 23), because 9% of the data points were missing. In contrast to repeated-measures analysis of variance, multilevel analysis handles incomplete data sets [29] and baseline differences between groups by allowing intercepts to vary between patients. A random intercept and slope model was used where repeated measurements (level 1) were nested within individual ACL patients (level 2). Thereafter, the following explanatory variables were added to the model: group (experimental, control [as a reference]), time (pre-surgery [as a reference], 5-weeks, 12-weeks, and 26-week post-surgery), and the group-by-time interaction. Sex was added as covariate for MVCs and hop distance in the (SPSS) model. The parameters of the multilevel model were estimated using the maximum-likelihood method. Only models with significantly better log likelihood values were retained. The analysis of the secondary outcomes was separately executed for the reconstructed leg, non-injured leg, and limb symmetry index (LSI). The LSI was calculated as: (reconstructed leg/non-injured leg) × 100%.

Additional multilevel analyses were performed to examine whether sex, limb dominance, and age affected the recovery after ACL surgery. The multilevel model was identical to the model above with the exception that the explanatory variable group was replaced by sex (male, female), injured leg (non-dominant, dominant), and age (old, young). For age, patients in the old group were ≥ 30 years and patients in the young group were < 30 years [7]. The outcomes of interest were the Hughston Clinic Knee score and LSIs for quadriceps MVCs, hamstring MVCs, and single leg hop distance.

Explanatory variables that significantly contributed to the model were subjected to a Bonferroni post hoc test to determine the means that were different. Cohen's *d* and 95% confidence intervals (CI) were calculated for significant effects. The level of significance (α) was set at $p < 0.05$.

An a priory power analysis was performed using G*Power 3.1 to calculate the sample size necessary to attain a significant effect of cross-education on the primary outcome measure (i.e., HCK score). The effect of cross-education on the HCK score has not been examined previously, and therefore, we used a small effect size of 0.2 for the power analysis to prevent underestimation of the sample size. Using an effect size of 0.20 with a power of 80% at the $p < 0.05$ significance level required a sample size of 36 (i.e., 18 patients per group). The aim was to recruit 25 patients per group to allow for dropouts.

Results

Primary outcome

Figure 1 shows the HCK scores for the experimental and control groups. A main effect of time was observed ($F_{3,121} = 66.6$, $p < 0.001$). Relative to pre-surgery, both groups showed self-reported knee function to be impaired 12% at 5-week post-surgery (95% CI 7–17, $p < 0.001$) and 15% improved at 26-week post-surgery (95% CI − 20 to − 10, $p < 0.001$).

Secondary outcomes

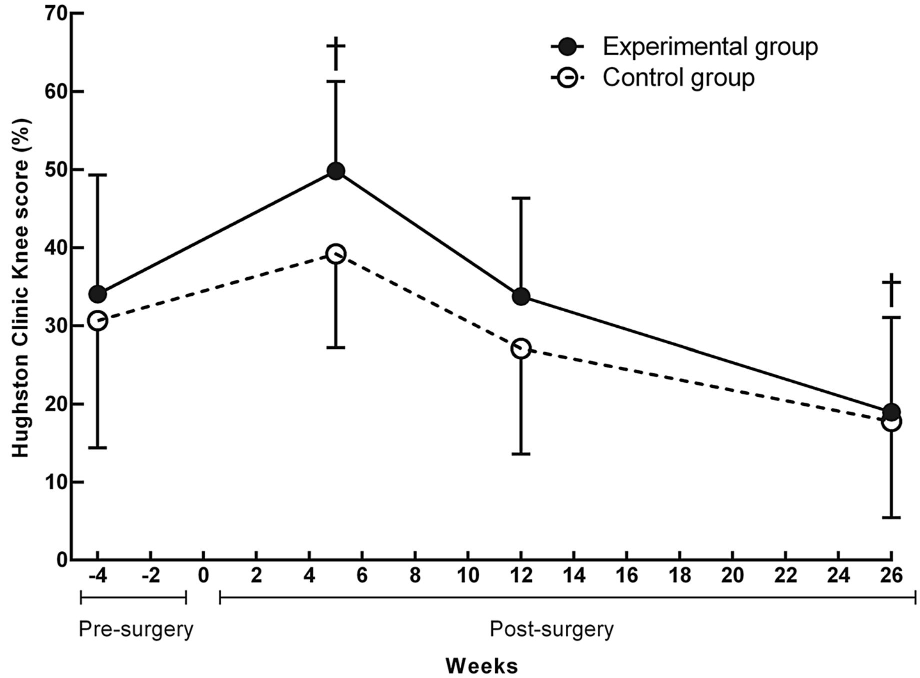
Maximal quadriceps' torque

Table 3 shows the quadriceps MVCs in the ACL patients' reconstructed and non-injured leg, including LSIs. Significant time effects were found for MVCs of the reconstructed leg, non-injured leg, and LSI. Relative to pre-surgery, quadriceps MVCs of the reconstructed leg were 38% decreased at 5-week post-surgery, 14–16% decreased at 12-week post-surgery, and 5–13% increased at 26-week post-surgery. The quadriceps' MVCs of the non-injured leg increased 3–8% at 5-week post-surgery, 8–12% at 12-week post-surgery, and 8–14% at 26-week post-surgery. LSIs were lower at 5-week and 12-week post-surgery compared to pre-surgery and were returned to pre-surgery level at 26-week post-surgery. Only the LSI of eccentric quadriceps MVCs was still lower at 26-week post-surgery.

Maximal hamstring torque

Table 4 shows the hamstring MVCs in the ACL patients' reconstructed and non-injured leg, including LSIs. No between-group differences were observed. Significant time effects were found for the reconstructed leg, non-injured leg, and LSI. Relative to pre-surgery, MVCs of the reconstructed leg showed 43% deficit at 5-week post-surgery, 21% deficit at 12-week post-surgery, and 8–9% improvement at 26-week post-surgery. Relative to pre-surgery, MVCs of the non-injured leg increased 8% at 12-week post-surgery and 7–18% at 26-week post-surgery. Compared to pre-surgery,

Fig. 1 Hughston Clinic Knee score of the experimental and control groups (mean ± SD). A higher score means worse self-reported knee function. †The scores in both groups were different compared to pre-surgery ($p < 0.05$)



the LSI of hamstring MVCs was worse at 5-week, 12-week, and 26-week post-surgery.

Single leg hop distance

Table 5 illustrates the single leg hop distance for the ACL-reconstructed and non-injured leg, including LSIs. There was a significant time effect for the non-injured leg ($p = 0.039$). Post hoc testing revealed that the hop distance was 2% increased at 26-week post-surgery compared to pre-surgery.

Effects of sex, limb dominance, and age on ACL recovery

Online Resource 2 shows the recovery after ACL surgery for males and females. A sex-by-time interaction was observed for the HCK score ($F_{3,121} = 3.3$, $p = 0.021$). Relative to pre-surgery, self-reported knee function was 10% worse for males than females at 5-week post-surgery (95% CI 3–18, $d = -0.80$), 10% worse at 12-week post-surgery (95% CI 2–18, $d = -0.80$), and 8% worse at 26-week post-surgery (95% CI 1–16, $d = -0.64$) (all $p \leq 0.034$). Online Resource 3 shows that ACL recovery was unaffected by whether the injured leg was the non-dominant or dominant leg (all n.s.). Online Resource 4 shows that ACL recovery was also not affected by age (all n.s.). Time effects are not reported here as they are already explained in the previous sections.

Discussion

The most important findings of the present study were that cross-education as an adjuvant to standard care did not improve ACL rehabilitation outcomes at 5-week, 12-week, and 26-week post-surgery. Nonetheless, 26 weeks of ACL rehabilitation improved self-reported knee function, maximal quadriceps and hamstring MVCs, and single leg hop distance in both groups relative to pre-surgery. Interestingly, self-reported knee function was 8–10% worse in males than females at each time point after surgery.

Primary outcome

Self-reported knee function was not different between the experimental and control groups which supports the idea that the cross-education effect is too small to meaningfully improve activities of daily living [5, 19]. However, there is also evidence to the contrary [27], but baseline differences and small (~ 8%) between-group differences after the intervention also question the clinical relevance of those data. Interestingly, females compared with males reported 8–10% better self-reported knee function in the first 6 months after surgery, but this between-sex difference is smaller than the 11% required to overcome the measurement error [4]. Thus, the clinical relevance of this sex difference is questionable, especially because poorer self-reported knee function was observed for females compared with males at 12–45 months post-surgery [33, 39]. Our pre and post-surgical scores on the HCK questionnaire were comparable to the previous research [15], were not influenced by limb dominance or

Table 3 Maximal quadriceps' torques and limb symmetry indices

Outcome	Groups							
	Pre-surgery		5-week post-surgery		12-week post-surgery		26-week post-surgery	
	Exp ($n=22$)	Con ($n=21$)	Exp ($n=22$)	Con ($n=21$)	Exp ($n=22$)	Con ($n=21$)	Exp ($n=22$)	Con ($n=21$)
Eccentric 60°/s								
Reconstructed leg (Nm/kg)	3.4 (1.0)	3.0 (0.9)	–	–	–	–	3.4 (1.4)	2.9 (1.1)
Non-injured leg (Nm/kg)	3.8 (0.8)	3.5 (1.0)	3.9 (1.2)	3.8 (1.0)	4.1 (1.2)	3.9 (1.2)	4.2 (1.3)	3.8 (1.1)
Limb symmetry index (%)	91 (19)	91 (23)	–	–	–	–	78 (16)	78 (19)
Isometric								
Reconstructed leg (Nm/kg)	3.4 (0.7)	3.0 (0.9)	2.0 (0.8)	2.0 (0.8)	2.7 (0.8)	2.7 (0.9)	3.5 (0.9)	3.2 (0.9)
Non-injured leg (Nm/kg)	3.7 (0.7)	3.5 (0.8)	3.8 (0.7)	3.6 (0.8)	3.9 (0.7)	3.8 (1.0)	4.0 (0.8)	3.9 (0.8)
Limb symmetry index (%)	93 (13)	85 (14)	52 (19)	54 (13)	68 (16)	70 (12)	88 (11)	83 (11)
Concentric (60°/s)								
Reconstructed leg (Nm/kg)	2.3 (0.7)	2.0 (0.6)	2.8 (0.6)	–	1.9 (0.8)	1.9 (0.7)	2.4 (0.8)	2.3 (0.6)
Non-injured leg (Nm/kg)	2.6 (0.7)	2.4 (0.5)	–	2.6 (0.6)	2.9 (0.6)	2.7 (0.7)	2.9 (0.7)	2.8 (0.6)
Limb symmetry index (%)	91 (23)	83 (15)	–	–	62 (19)	68 (15)	81 (11)	80 (12)
Concentric (120°/s)								
Reconstructed leg (Nm/kg)	1.9 (0.7)	1.8 (0.5)	–	–	1.7 (0.6)	1.7 (0.6)	2.0 (0.6)	2.0 (0.5)
Non-injured leg (Nm/kg)	2.3 (0.6)	2.0 (0.5)	2.2 (0.5)	2.1 (0.5)	2.4 (0.5)	2.3 (0,5)	2.4 (0.5)	2.3 (0.5)
Limb symmetry index (%)	87 (23)	91 (18)	–	–	69 (18)	74 (14)	83 (12)	83 (11)
Concentric (180°/s)								
Reconstructed leg (Nm/kg)	1.7 (0.6)	1.6 (0.4)	–	–	1.6 (0.5)	1.5 (0.5)	1.8 (0.5)	1.8 (0.5)
Non-injured leg (Nm/kg)	2.0 (0.6)	1.8 (0.5)	2.0 (0.5)	1.9 (0.5)	2.1 (0.5)	2.1 (0.5)	2.1 (0.5)	2.1 (0.4)
Limb symmetry index (%)	87 (18)	88 (13)	–	–	75 (16)	75 (12)	88 (12)	85 (11)

Outcome	Difference within groups						Difference between groups		
	5-week minus pre-surgery		12-week minus pre-surgery		26-week minus pre-surgery		5-week minus pre-surgery	12-week minus pre-surgery	26-week minus pre-surgery
	Exp	Con	Exp	Con	Exp	Con	Exp–Con	Exp–Con	Exp–Con
Eccentric (60°/s)									
Reconstructed leg (Nm/kg)	–	–	–	–	0.1 (0.9)	−0.1 (0.5)	–	–	−0.2 (−0.6 to 0.2)
Non-injured leg (Nm/kg)	0.3 (0.6)†	0.4 (0.5)†	0.4 (0.6)†	0.5 (0.6)†	0.6 (0.6)†	0.3 (0.5)†	0.1 (−0.2 to 0.4)	0.1 (−0.3 to 0.4)	−0.3 (−0.6 to 0.1)
Limb symmetry index (%)	–	–	–	–	−14 (23)†	−12 (22)†	–	–	2 (−12 to 16)
Isometric									
Reconstructed leg (Nm/kg)	−1.3 (0.6)†	−1.0 (0.5)†	−0.6 (0.6)†	−0.3 (0.5)†	0.2 (0.6)	0.3 (0.5)†	0.3 (0.0 to 0.7)	0.3 (0.0 to 0.6)	0.0 (−0.3 to 0.4)
Non-injured leg (Nm/kg)	0.3 (0.4)†	0.1 (0.3)	0.4 (0.4)†	0.4 (0.4)†	0.5 (0.4)†	0.4 (0.3)†	−0.1 (−0.3 to 0.1)	0.0 (−0.2 to 0.2)	−0.1 (−0.3 to 0.1)
Limb symmetry index (%)	−41 (14)†	−31 (12)†	−24 (14)†	−15 (12)†	−6 (15)	−2 (12)	10 (2 to 18)	9 (1 to 17)	4 (−5 to 12)
Concentric (60°/s)									
Reconstructed leg (Nm/kg)	–	–	−0.4 (0.4)†	−0.2 (0.4)†	0.1 (0.4)	0.2 (0.4)†	–	0.2 (0.0 to 0.5)	0.1 (−0.1 to 0.4)

Table 3 (continued)

Outcome	Difference within groups						Difference between groups		
	5-week minus pre-surgery		12-week minus pre-surgery		26-week minus pre-surgery		5-week minus pre-surgery	12-week minus pre-surgery	26-week minus pre-surgery
	Exp	Con	Exp	Con	Exp	Con	Exp–Con	Exp–Con	Exp–Con
Non-injured leg (Nm/kg)	0.2 (0.4)†	0.1 (0.2)†	0.3 (0.4)†	0.2 (2.3)†	0.4 (0.4)†	0.4 (2.3)†	−0.1 (−0.3 to 0.1)	−0.1 (−0.3 to 0.1)	0.0 (−0.2 to 0.2)
Limb symmetry index (%)	–	–	−27 (22)†	−15 (14)†	−9 (24)	−3 (13)	–	12 (1 to 23)	6 (−5 to 17)
Concentric (120°/s)									
Reconstructed leg (Nm/kg)	–	–	−0.2 (0.5)	−0.1 (0.3)	0.2 (0.6)	0.2 (0.3)†	–	0.1 (−0.2 to 0.3)	−0.1 (−0.3 to 0.2)
Non-injured leg (Nm/kg)	0.1 (0.2)	0.1 (3.2)	0.2 (0.2)†	0.2 (3.2)†	0.3 (0.3)†	0.3 (2.3)†	0.1 (−0.1 to 0.2)	0.0 (−0.1 to 0.2)	0.0 (−0.2 to 0.2)
Limb symmetry index (%)	–	–	−17 (24)†	−18 (19)†	−4 (26)	−8 (18)†	–	0 (−14 to 13)	−5 (−18 to 9)
Concentric (180°/s)									
Reconstructed leg (Nm/kg)	–	–	−0.1 (0.4)	0.0 (0.3)	0.2 (0.5)†	0.2 (0.3)†	–	0.1 (−0.1 to 0.3)	0.0 (−0.2 to 0.2)
Non-injured leg (Nm/kg)	0.1 (0.2)	0.1 (0.2)†	0.2 (0.2)†	0.2 (0.2)†	0.3 (0.2)†	0.3 (0.2)†	0.1 (−0.1 to 0.2)	0.1 (−0.1 to 0.2)	0.0 (−0.1 to 0.2)
Limb symmetry index (%)	–	–	−12 (18)†	−13 (14)†	0 (19)	−3 (13)	–	−1 (−11 to 8)	−3 (−13 to 7)

Mean (SD) of each group, mean (SD) difference within each group, and mean (95% CI) difference between groups

Exp Experimental group, *Con* control group

†Different compared to pre-surgery ($p < 0.05$)

Table 4 Maximal hamstring torques and limb symmetry indices

Outcome	Groups							
	Pre-surgery		5-week post-surgery		12-week post-surgery		26-week post-surgery	
	Exp ($n=22$)	Con ($n=21$)	Exp ($n=22$)	Con ($n=21$)	Exp ($n=22$)	Con ($n=21$)	Exp ($n=22$)	Con ($n=21$)
Eccentric (60°/s)								
Reconstructed leg (Nm/kg)	2.1 (0.6)	1.9 (0.6)	–	–	–	–	2.3 (0.5)	1.9 (0.5)
Non-injured leg (Nm/kg)	2.5 (0.6)	2.3 (0.5)	2.6 (0.5)	2.3 (0.7)	2.6 (0.5)	2.4 (0.7)	2.6 (0.5)	2.4 (0.7)
Limb symmetry index (%)	90 (15)	86 (20)	–	–	–	–	87 (10)	83 (13)
Isometric								
Reconstructed leg (Nm/kg)	1.5 (0.3)	1.3 (0.4)	0.8 (0.3)	0.8 (0.4)	1.0 (0.4)	1.1 (0.5)	1.3 (0.3)	1.3 (0.5)
Non-injured leg (Nm/kg)	1.6 (0.3)	1.4 (0.4)	1.5 (0.3)	1.5 (0.4)	1.5 (0.3)	1.6 (0.5)	1.6 (0.3)	1.6 (0.5)
Limb symmetry index (%)	93 (14)	91 (21)	54 (18)	56 (14)	70 (20)	72 (13)	80 (16)	80 (13)
Concentric (60°/s)								
Reconstructed leg (Nm/kg)	1.2 (0.3)	1.1 (0.4)	–	–	1.0 (0.4)	1.1 (0.4)	1.3 (0.4)	1.3 (0.5)
Non-injured leg (Nm/kg)	1.3 (0.3)	1.2 (0.3)	1.4 (0.3)	1.3 (0.4)	1.4 (0.3)	1.3 (0.4)	1.5 (0.4)	1.5 (0.5)
Limb symmetry index (%)	94 (16)	92 (18)	–	–	71 (21)	83 (11)	85 (13)	89 (13)
Concentric (120°/s)								
Reconstructed leg (Nm/kg)	1.2 (0.3)	1.0 (0.3)	–	–	1.0 (0.3)	1.0 (0.5)	1.2 (0.3)	1.2 (0.4)
Non-injured leg (Nm/kg)	1.2 (0.3)	1.0 (0.3)	1.2 (0.3)	1.1 (0.5)	1.2 (0.3)	1.2 (0.4)	1.4 (0.4)	1.3 (0.4)
Limb symmetry index (%)	99 (13)	96 (19)	–	–	79 (22)	86 (16)	88 (13)	91 (14)
Concentric (180°/s)								
Reconstructed leg (Nm/kg)	1.1 (0.3)	1.0 (0.3)	–	–	0.9 (0.3)	1.0 (0.5)	1.2 (0.3)	1.1 (0.4)
Non-injured leg (Nm/kg)	1.2 (0.3)	1.0 (0.3)	1.2 (0.3)	1.1 (0.4)	1.2 (0.3)	1.1 (0.4)	1.2 (0.3)	1.3 (0.4)
Limb symmetry index (%)	95 (13)	100 (29)	–	–	81 (20)	90 (17)	95 (18)	89 (12)

Outcome	Difference within groups						Difference between groups		
	5-week minus pre-surgery		12-week minus pre-surgery		26-week minus pre-surgery		5-week minus pre-surgery	12-week minus pre-surgery	26-week minus pre-surgery
	Exp	Con	Exp	Con	Exp	Con	Exp–Con	Exp–Con	Exp–Con
Eccentric (60°/s)									
Reconstructed leg (Nm/kg)	–	–	–	–	0.2 (0.6)	0.0 (0.4)	–	–	−0.2 (−0.5 to 0.1)
Non-injured leg (Nm/kg)	0.1 (0.4)	0.0 (0.3)	0.2 (0.4)	0.1 (0.3)	0.2 (0.4)	0.1 (0.3)	−0.1 (−0.3 to 0.1)	0.0 (−0.3 to 0.2)	−0.1 (−0.3 to 0.1)
Limb symmetry index (%)	–	–	–	–	−3 (20)	−3 (15)	–	–	1 (−10 to 12)
Isometric									
Reconstructed leg (Nm/kg)	−0.6 (0.3)†	−0.5 (0.3)†	−0.4 (0.3)†	−0.2 (0.3)†	−0.1 (0.3)	0.0 (0.3)	0.1 (−0.1 to 0.3)	0.2 (0.0 to 0.3)	0.1 (0.0 to 0.3)
Non-injured leg (Nm/kg)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.1 (0.2)†	0.1 (0.3)	0.2 (0.2)†	0.0 (−0.1 to 0.2)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)
Limb symmetry index (%)	−38 (21)†	−36 (18)†	−22 (21)†	−20 (18)†	−11 (22)	−12 (17)†	2 (−9 to 14)	2 (−9 to 14)	−1 (−13 to 11)
Concentric (60°/s)									
Reconstructed leg (Nm/kg)	–	–	−0.2 (0.3)†	0.0 (0.2)	1.0 (0.3)	0.2 (0.2)†	–	0.2 (0.0 to 0.3)	0.1 (0.0 to 0.3)
Non-injured leg (Nm/kg)	0.1 (0.2)	0.1 (0.3)	0.1 (0.2)	0.1 (0.3)	0.2 (0.2)†	0.3 (0.3)†	0.0 (−0.2 to 0.1)	0.0 (−0.1 to 0.2)	0.1 (0.0 to 0.3)
Limb symmetry index (%)	–	–	−22 (21)†	−10 (17)†	−8 (22)	−3 (17)	–	12 (1 to 24)	5 (−7 to 16)

Table 4 (continued)

Outcome	Difference within groups						Difference between groups		
	5-week minus pre-surgery		12-week minus pre-surgery		26-week minus pre-surgery		5-week minus pre-surgery	12-week minus pre-surgery	26-week minus pre-surgery
	Exp	Con	Exp	Con	Exp	Con	Exp–Con	Exp–Con	Exp–Con
Concentric (120°/s)									
Reconstructed leg (Nm/kg)	–	–	−0.2 (0.3)†	0.0 (0.3)	1.0 (0.3)	0.2 (0.3)†	–	0.2 (0.0 to 0.4)	0.1 (−0.1 to 0.3)
Non-injured leg (Nm/kg)	0.1 (0.2)	0.1 (0.3)	0.1 (0.2)	0.1 (0.3)	0.2 (0.2)†	0.3 (0.3)†	0.0 (−0.2 to 0.2)	0.1 (−0.1 to 0.2)	0.1 (−0.1 to 0.2)
Limb symmetry index (%)	–	–	−19 (22)†	−10 (21)	−9 (23)	−5 (20)	–	9 (−4 to 22)	4 (−9 to 18)
Concentric (180°/s)									
Reconstructed leg (Nm/kg)	–	–	−0.2 (0.3)†	0.0 (0.3)	0.1 (0.3)	0.1 (0.3)	–	0.2 (0.0 to 0.4)	0.0 (−0.1 to 0.2)
Non-injured leg (Nm/kg)	0.0 (0.2)	0.1 (0.3)	0.0 (0.2)	0.1 (0.3)	0.1 (0.2)	0.3 (0.3)†	0.1 (0.0 to 0.3)	0.1 (0.0 to 0.3)	0.2 (0.0 to 0.3)
Limb symmetry index (%)	–	–	−14 (24)†	−10 (27)	0 (25)	−12 (26)	–	3 (−13 to 18)	−12 (−28 to 3)

Mean (SD) of each group, mean (SD) difference within each group, and mean (95% CI) difference between groups

Exp Experimental group, *Con* control group

†Different compared to pre-surgery ($p < 0.05$)

age, and reflect a clinically relevant improvement (15%) in subjective knee function at 26 week post-surgery vs. pre-surgery.

Maximal quadriceps' torque

This is the first study designed to specifically examine the long-term effects of cross-education training in patients after ACL reconstruction. Unlike in a previous study at 8 weeks after ACL reconstruction [26], the present study found no cross-education effects at any point up to 26 weeks after surgery in the reconstructed and non-injured leg for quadriceps MVCs. How and if at all it was cross-education that improved quadriceps strength is unclear because, unlike the previous cross-education studies [5, 20], cross-education occurred in the absence of a training effect in the trained leg [26]. In healthy adults, the effects of cross-education on maximal voluntary muscle strength can last up to 12 weeks [16] and in patients up to 26 weeks after a wrist fracture [19]. The absence of a cross-education effect in the present study made it not possible to compare the time course of cross-education between patients and healthy adults.

The rate of change in quadriceps MVC torques showed a different pattern in the two legs. The reconstructed leg showed a 38% deficit at 5-week post-surgery relative to pre-surgery, but this deficit diminished and was 14–16% at 12-week post-surgery and changed into 5–13% improvement at 26-week post-surgery. In contrast, the non-injured leg showed a monotonic 3–14% increase from pre-surgery to 26-week post-surgery. Five patients where operated using the patellar tendon instead of the hamstring tendon as autograft which could have negatively influenced the overall quadriceps MVC results [21]. The LSIs for the different contraction types were 78–86% at 26-week post-surgery, meaning that most patients did not meet yet the LSI criterion of ≥ 90% to safely return to sports [12, 24]. The recovery of quadriceps MVCs did not differ between sexes confirming the previous research [33] and was not affected by age, a factor that has not been systematically examined yet. Only a handful of studies report the time course of MVC torques after ACL surgery [6, 14, 17], so our data elucidate the longitudinal strength development of the reconstructed and non-injured leg.

Maximal hamstring torque

The cross-education effect is muscle specific [3], so it was expected that cross-education training for the quadriceps would not further improve hamstring MVCs. Thirty-seven subjects received a hamstring tendon autograft for ACL reconstruction and the ensuing hamstring weakness was not unexpected [21]. Relative to pre-surgery, hamstring torque deficits for the reconstructed leg of 43% and 21% were observed, respectively, 5-week and 12-week post-surgery. The reconstructed and non-injured leg improved 7–18% in hamstring MVCs at 26-week post-surgery vs. pre-surgery, and these MVCs were comparable to never-injured, active controls [42]. As shown before [33], sex did not affect the recovery of hamstring strength as assessed by MVCs and this study now shows, for the first time, that age and limb dominance also did not affect this recovery.

Although hamstring MVCs were comparable to controls at 26-week post-surgery, LSIs for eccentric and isometric MVCs were below the satisfactory 90% [35]. The lowest LSIs were observed for isometric MVCs, but these values were not different compared to the previous research [14, 17]. The low LSIs for isometric MVCs are likely caused by the harvested hamstring tendon that has a more severe effect on the torque production at deeper knee-flexed positions (i.e., peak torques are attained at higher knee flexion for isometric contractions than for eccentric and concentric contractions) [23].

Single leg hop distance

The hop distance, measured before and 26 weeks after surgery, did not differ between groups and was comparable to the previous research [6, 30]. The hop test simulates loads encountered during sport-specific movements where an LSI of > 90% is a criterion for return to sports [35]. Not surprisingly, our ACL patients, at 26-week post-surgery, were not yet ready to return to sports with an LSI of 86%. The LSI for hop distance was not affected by whether the injured leg was the dominant or non-dominant leg. Lower LSIs are observed for females and ACL patients > 25 years at 14-month post-surgery [39], but we did not find such effects at 26-week post-surgery. However, the LSI for single leg hop distance should be interpreted with caution, because both legs showed deficits at 7-month post-surgery compared to normative data reported for healthy controls [11]. Quadriceps' strength is a strong predictor of hop test performance [32], but the increase in quadriceps' strength observed in the present study was not enough to produce a clinically meaningful increase in single leg hop distance of 7% [30].

Only knee extensor exercises were part of our cross-education protocol, because quadriceps' weakness is often associated with functional impairments after ACL reconstruction [32]. However, a cross-education intervention that also targets hamstring strength could be of additive value for the recovery after ACL reconstruction, because hamstring weakness can persist up to 24 months after ACL surgery [6, 17]. Targeting the hamstrings is also relevant, because a 25% reduction in hamstring strength can increase ACL loading by 36% during sidestep cutting [40] and because females with reduced hamstring strength prior to an ACL injury were more likely to rupture their ACL [22].

Strict inclusion and exclusion criteria were applied, but the inter-subject variability was still high. The cross-education training might have caused subtle differences in primary and secondary outcome measures, but these remain unnoticed due to the high inter-subject variability. Future studies should examine the cross-education effect in more homogeneous clinical populations to conclude more firmly whether cross-education training can be meaningful in the rehabilitation from unilateral orthopedic and neurological impairments.

To implement cross-education training in ACL practice, the training load of the cross-education protocol should be higher than in the present study to induce strength gains in the non-injured and reconstructed leg. Interventions like cross-education that target quadriceps and hamstring weakness after ACL reconstruction are necessary as data from the traditional ACL rehabilitation programs are concerning. To illustrate, discharge criteria for hamstring and quadriceps strength are only met by 21% of the patients at 9-month post-surgery [41] and by 28% of the patients at the time of

Table 5 Single leg hop distances and limb symmetry indices

Outcome	Groups				Difference within groups		Difference between groups
	Pre-surgery		26-week post-surgery		26-week minus pre-surgery		26-week minus pre-surgery
	Exp (n = 18)	Con (n = 16)	Exp (n = 18)	Con (n = 16)	Exp	Con	Exp–Con
Reconstructed leg (m)	124 (38)	113 (37)	121 (42)	120 (35)	6 (36)	2 (18)	− 4 (− 23 to 15)
Non-injured leg (m)	147 (33)	130 (31)	144 (33)	139 (28)	3 (15)	9 (15)[†]	6 (− 5 to 17)
Limb symmetry index (%)	84 (17)	86 (13)	86 (18)	85 (13)	3 (21)	− 4 (9)	− 6 (− 17 to 5)

Mean (SD) of each group, mean (SD) difference within each group, and mean (95% CI) difference between groups

Exp Experimental group, *Con* control group

[†]Different compared to pre-surgery ($p < 0.05$)

return to sports [36]. Leaving these strength deficits untargeted increases the risk of rerupturing the ACL [13]. Cross-education training could decrease quadriceps and hamstring weakness in the early phase after ACL reconstruction, making it more likely that patients meet the strength criteria for safe return to sports in the later phase of rehabilitation.

Conclusions

This randomized controlled clinical trial shows that cross-education in the early phase after ACL reconstruction did not improve rehabilitation outcomes. The training load of the cross-education program was not high enough as cross-education training did not induce extra strength gains in the quadriceps muscles of the non-injured leg. Nonetheless, irrespective of the adjuvant cross-education training, improvements in self-reported knee function, quadriceps strength, and hamstring strength were observed at 26-week post-surgery compared to pre-surgery. Cross-education had no negative influence on ACL recovery and could supposedly still accelerate the ACL recovery when training load of the cross-education protocol is increased.

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Compliance with ethical standards

Conflict of interest The authors report that no conflicts of interest have occurred that are associated with the current study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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