Progressive Supervised Home-based Strength Training in Children With Spastic Cerebral Palsy

NCT number: NCT03863197

Protocol data: 1 November 2021

Study protocol

Study outline

A waitlist randomized controlled trial (RCT) will be conducted to define the effects of a progressive resistance training (PRT) program for the knee extensor, knee flexor and plantar flexor muscle groups in children with spastic cerebral palsy (CP). A minimization technique will be used to divide participants in an intervention group, performing a 12-week PRT program and a waitlist control group, continuing usual care for 12 weeks first. After the control period, the participants were offered to participate in the intervention.

Participants

Participants will be recruited across Flanders in Belgium, through the CP reference center of the University Hospitals Leuven, pediatric physiotherapists, and special needs schools. Written informed consent will be obtained from the children's parents or legal guardian prior to the first assessment. The study is registered at Clinicaltrials.gov (NCT03863197) and was approved by local medical ethical committees of University Hospitals Leuven (s59945) and Ghent (EC/2017/0526). The inclusion criteria for participation are 1) a diagnosis of SCP, 2) age at baseline between 5 and 11 years and 3) level of I, II or III on the gross motor function classification system (GMFCS) (Palisano et al., 2008) . Exclusion criteria were 1) botulinum neuro-toxin A injections and/or lower leg casts in the past 6 months, 2) lower limb bony surgery in the past 2 years, 3) lower limb muscular surgery or selective dorsal rhizotomy at any time point, 4) inability to communicate in Dutch or English and 5) inability to understand instructions and cooperate during assessments and training.

For comparison of baseline data, a convenience sample of typically developing (TD) children will be recruited via hospital co-workers and students within the same age range of 5–12 years. The TD children could not have any known neurological or orthopedic lower limb problems. The TD children will only participate in one assessment of isometric strength, 3D freehand ultrasonography and functional strength (see below).

Study design

After enrollment and prior to the first assessment, participants will be assigned to the intervention or the control group through randomization by minimization. MinimPy will be used to randomize the participants based on age (2 levels: <8 years and >8 years) and GMFCS score (3 levels: I, II and III) (Saghaei, 2011). The allocation ratio will be 1:1 with probability set at 0.75. The biased coin minimization will be used as probability method and marginal balance as distance measure.

Assessments are planned in the University Hospitals and special needs schools, at baseline (PRE) and after the 12-week control or intervention period (POST). Training and assessments will always be

conducted on different days. Participants in the intervention group start training within 2 weeks after the baseline assessment. For both groups, the POST assessments will be performed within 1 week after the 12-week period. Blinding is not completely possible since participants and trainers are aware of group allocation. Assessors are also aware of group allocation during assessments but data will be anonymized before processing and analyses. The participants will be assessed by the same assessors (PRE and POST) and the data of one participant will be processed by the same processer.

Piloting for the feasibility of the measurements and parameter extraction was done through prior and parallel investigations. The exercises used during the training were piloted through iterations with strength and conditioning specialists to ensure correct exercise selection and also with senior pediatric physiotherapists and their patients to ensure the applicability in targeted population of children with SCP.

Sample size

At the moment of trial design (2018), no data were available on an RCT investigating changes in muscle size after PRT in a population of children with SCP. Therefore, effect sizes (d) of systematic reviews and meta-analyses reporting muscle strength outcomes after PRT were used. Reported effect sizes were moderate (d=0.53) (Ryan et al., 2017) and large (d=1.050 and d=1.105) (Park & Kim, 2014). Based on a large effect size of d=0.8 with the probability of making a type I error set equal to or less than 1% ($p \leq 0.01$) and a power of 80%, an independent samples t-test with common standard deviation required 39 independent observations per group to compare the evolution over time between the intervention and control groups. To account for the possibility of clustered legs in bilaterally affected participants a design effect (Killip et al., 2004) was calculated resulting in an estimated sample size of clustered observations per group with following formulas:

Design effect = 1 + ρ(m-1),*

where ρ is the intraclass correlation and m the cluster size, and,

*Estimated sample size of clustered legs = estimated sample size of independent observations * design effect = m * number of participants*

With a cluster size of m=2 (2 legs per bilaterally affected participant) and an intraclass correlation coefficient of $\rho=0.1$, based on literature of general health parameters (Adams et al., 2004), the estimated design effect was 1.1, resulting in 43 clustered legs, or 22 bilaterally affected participants per group. A group including both uni- and bilaterally affected children would require a sample size between 39 and 43.

Intervention

Participants assigned to the control group will continue their usual care. Participants assigned to the intervention group will undertake 3 to 4 PRT sessions per week (alternating), on non-consecutive days, for 12 weeks, resulting in a total of 42 scheduled sessions. The PRT program will be explained during a visit to the physiotherapist(s) and parent(s). After a familiarization phase of up to 3 sessions, the official PRT starts. At least 1 session per week will be performed under the supervision of the physiotherapist(s). The remaining sessions will be completed at home under the supervision of a parent or guardian. We will create a patient-specific PRT program through the online software platform Skill-Up (www.Skill-up.com) and ask the participants to log each PRT session in a training diary. Throughout the 12-week period, the PRT program will be supervised through phone calls, e-mails, and targeted visits to check adherence and progress exercises by trainers with a background in human movement sciences. Participants in the intervention group were invited for an interim

assessment after 6 weeks, which was also used as an additional moment to evaluate and adjust the intensity of the training program.

The PRT program, targeting strength and hypertrophy of knee extensors, knee flexors and plantar flexors, will be prescribed in close consultation with the personal physiotherapist(s) to ensure feasibility for each participant. The general session design recommendations include a 5-minute dynamic warm-up and a 5-minute cool-down. Depending on the participants' abilities, the PRT will start with 1-3 functional multi-joint exercises, followed by 2-3 single-joint exercises targeting the specific muscle groups, all performed without orthotics. Following international guidelines for youth resistance training of the National Strength and Conditioning Association, as well as CP-specific recommendations, the initial exercises start at a training volume of 3 sets of 10 repetitions, aiming at an exercise intensity of 60 to 80% of the estimated 1-repetition maximum, with a rest period in between sets of at least 1 minute (Faigenbaum et al., 2009; Lloyd et al., 2014; Noorduyn et al., 2011; Verschuren et al., 2016). The most difficult exercise that could be performed, with the maximal load that could be lifted, for the defined number of repetitions and sets was defined through trial and error (Moreau, 2020). Throughout the training program, exercise difficulty was increased. Thereto, physiotherapists will be encouraged to regularly test the difficulty of the exercises, i.e. at least biweekly, by asking a maximum performance in the last set, based on exercise execution and fatigue. The intensity will be modified by the trainers or the physiotherapist(s) if the last set exceeded 15 well-executed repetitions. Exercise modification options are dependent on the exercise and include addition of weight in a weighted vest (0.5kg increments up to 10kg), use of a stronger resistance band (5 colors ranging from light to very heavy), increase of ankle weight (1.0, 1.5 or 2.0kg), or selection of a more challenging exercise. The number of sets and repetitions performed, modifications or compensations, perceived fatigue at the end of the session and potential adverse events will be noted in the training diary.

Assessments and outcome measures

1. Participant characteristics

Age, body mass and height will be recorded for the participants at each assessment. Usual care and treatment history will be recorded at the PRE-assessment using standardized in-house questionnaires. A routine clinical examination regarding the investigated muscle groups will be performed, including passive joint range of motion, spasticity, manual muscle strength and selective motor control (SMC), based on standard clinical scales (Bohannon & Smith, 1987; Boyd, 1999; Gage et al., 2009; Matthews, 1977). These clinical examination parameters will be used to define the most affected leg for bilaterally affected children. If both sides are equally affected, the right leg will be used. Lower limb SMC will be assessed with the selective control assessment of the lower extremity total limb score (Fowler et al., 2009). Assessments will be performed in the same order, starting with clinical examination and muscle morphology, followed by isometric and functional strength and lastly gross motor function and walking capacity.

2. Isometric strength assessments

Knee extensor, knee flexor and plantar flexion maximum voluntary isometric contractions were collected with a fixed dynamometer in a previously described, custom-designed chair (Goudriaan et al., 2018). The dynamometer is positioned at 75% of the lower leg and foot length, and the level arm distance is measured between this position and the joint axis. After a test trial, we aim to collect 3 well executed maximum voluntary isometric contractions with a duration of 3 to 5 seconds. Standardized verbal encouragement and visual feedback will be provided throughout the isometric contraction. The protocol includes periods of rests of at least 10 seconds between repeated

assessments and of at least 2 minutes between different muscle groups. Peak force is extracted from each trial with a custom-written MATLAB script and maximal joint torque (in Nm) will be calculated by multiplying peak force with the lever arm and taking the average of the 3 trials. Knee and plantar flexion maximal voluntary isometric contractions are corrected for gravity by subtracting the gravitational torque in rest from the outcomes. Maximal joint torque will be normalized by dividing it by body weight (Nm/kg).

3. Three-dimensional freehand ultrasonography

A previously validated 3-dimensional freehand ultrasonography technique will be used to evaluate muscle morphology, combining a 2-dimensional B-mode ultrasonography device (Telemed-Echoblaster 128 Ext-1Z, with a 5.9 cm 10MHz linear ultrasound transducer, Telemed, Ltd, Lithuania) with a motion tracking system (Optitrack V120:Trio, NaturalPoint, Inc, Corvallis, Oregon, USA) (Cenni et al., 2016). Ultrasound settings will be kept constant throughout the study period, at a frequency of 8MHz, with a focus of 3cm, a gain of 64%, a dynamic range of 56 dB and unaltered time-gain compensation. Depth can vary between 5cm and 7cm, adjusted to muscle size. The m. rectus femoris and m. tibialis anterior will be scanned in supine position with a triangular cushion underneath the calf, providing approximately 25 degrees of knee and hip flexion. The m. semitendinosus and m. medial gastrocnemius will be scanned in prone position with a triangular cushion underneath the shank, providing 25 degrees of knee flexion and an unconstrained ankle angle. STRADWIN software (version 6.0; Mechanical Engineering, Cambridge University, Cambridge, UK) will be used for data acquisition, generation of 3-D datasets, and data processing. Data processing will be performed by experienced processers, drawing equally spaced transverse plane segmentations throughout the 3-D datasets, which will be interpolated with an automatic cubic planimetry technique resulting in the muscle volume (in mL) (Treece et al., 1999). Muscle length (in mm) will be defined by calculating the linear distance between muscle origin and muscle tendon junction. Both muscle volume and muscle length will be normalized to fibula length to correct for skeletal growth (mL/cm and cm/cm). The echo-intensity (EI) from ultrasound images will be used as an indication of intrinsic muscle quality, with higher EI-values representing an increased ratio of non-contractile vs. contractile tissue (Pitcher et al., 2015; Young et al., 2015). EI (expressed in arbitrary units) will be computed as the average value throughout the interpolated reconstruction of the muscle.

4. Functional strength assessments

Endurance functional strength will be as assessed with 30-s repetition maximum tests including bi- and unilateral heel raise, sit-to-stand, and lateral step-up, as previously described (van Tittelboom et al., 2021). Participants completed as many repetitions as possible in 30 seconds. Each test will be 3 times and the average taken as final score. Explosive strength will be evaluated with a standing long jump, with both feet together, which will also be repeated 3 times and the scores averaged. The use of orthoses will not be allowed, as the PRT program will also be performed without orthoses.

5. Gross motor function and walking capacity

Gross motor function will be evaluated with the Gross Motor Function Measure-Item Set (Brunton & Bartlett, 2011) and the Gross Motor Ability Estimator 2 used to estimate the final score. The 1-minute walk test, performed on an indoor 20-m track, will be used to assess walking capacity (Chrysagis et al., 2014; Mcdowell et al., 2009). The participant will be instructed to walk as fast as possible without running and the distance covered in 1 minute will be recorded. Both assessments will be performed without orthoses, but a kay-walker is allowed for the 1-minute walk test for children classified as GMFCS-level III.

6. Statistics

Descriptive statistics for all groups will summarized using appropriate summary indices. The comparison between TD children and children with CP will be performed with a Student's *t*-test (after confirming equality of variances) or the Mann–Whitney *U*-test. Associations between muscle morphology measures, muscle strength and participant characteristics will be evaluated with univariate linear regressions followed by a multivariate linear regression using a backward approach. The linear regressions in the TD cohort based on an anthropometric variable will be used to define the deficits in muscle strength and muscle morphology in CP children.

To define the effects of the PRT intervention linear mixed models will be applied to evaluate the difference in evolution over time between the control and intervention group (time*group interaction effect) and between PRE and POST within each group (time effect). The random effects in these models can correct for the correlation between repeated observations within the same subject. Moreover, in the case of missing values that are completely at random, i.e. not related to any observed or unobserved outcomes, or at random, i.e. related to observed outcomes, linear mixed models provide valid inferences for missing observations. A covariance structure for repeated measurements to model longitudinal dependencies within the participant will be applied with a random intercept for participant (legs are nested within participants). The models will be adjusted for age and GMFCS level as covariates as these were used to allocate the children to the control or intervention group. Age was entered as a categorical variable (<8 years and >8 years). A full-factorial time*group mean model adjusted for age and GMFCS level, with a compound symmetry covariance matrix, unless an unstructured covariance matrix results in a better fit (Akaike information criterion decrease of >2). Adjustment for age (categorical variable: <8 years and >8 years) and GMFCS level will be included as these were used to allocate the children to the control or intervention group.

The α-level will be adjusted to p≤0.01 since multiple parameters are evaluated for most research questions, with a maximum of 5 parameters (functional strength). All analyses will be performed with SPSS (Version 28, SPSS Inc., Chicago, Illinois).

Finally, the data of the total intervention group (intervention + waitlist control group with delayed intervention) will be used to define the association between baseline properties and the changes in the outcome parameters after PRT with uni- or multivariate regression (mixed) models.

References

Adams, G., Gulliford, M. C., Ukoumunne, O. C., Eldridge, S., Chinn, S., & Campbell, M. J. (2004). Patterns of intra-cluster correlation from primary care research to inform study design and analysis. *Journal of Clinical Epidemiology*, *57*(8), 785–794. https://doi.org/10.1016/j.jclinepi.2003.12.013

Bohannon, R. W., & Smith, M. B. (1987). Inter rater reliability of a modified Ashworth Scale of muscle spasticity. *Phys Ther*, *67*, 206–207. https://doi.org/10.1007/978-1-4471-5451-8_105

Boyd, R. (1999). Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. *Eur J Neurol*, *6*(suppl 4), 1–13. https://doi.org/10.1111/j.1468-1331.1999.tb00031.x

Brunton, L. K., & Bartlett, D. J. (2011). Validity and reliability of two abbreviated versions of the gross motor function measure. *Physical Therapy*, *91*(4), 577–588. https://doi.org/10.2522/ptj.20100279

Cenni, F., Monari, D., Desloovere, K., Erwin, A., Schless, S., & Bruyninckx, H. (2016). The reliability and validity of a clinical 3D freehand ultrasound system. *Computer Methods and Programs in Biomedicine*, *136*, 179–187.

Chrysagis, N., Skordilis, E. K., & Koutsouki, D. (2014). Validity and Clinical Utility of Functional Assessments in Children With Cerebral Palsy. *Archives of Physical Medicine and Rehabilitation*, *95*(2), 369–374. https://doi.org/10.1016/j.apmr.2013.10.025

Faigenbaum, A. D., Kraemer, W. J., Blimkie, C. J. R., Jeffreys, I., Micheli, L. J., Nitka, M., & Rowland, T. W. (2009). Youth resistance training: updated position statement paper from the national strength and conditioning association. In *Journal of strength and conditioning research / National Strength & Conditioning Association* (Vol. 23, Issue 5 Suppl, pp. S60–S79). https://doi.org/10.1519/JSC.0b013e31819df407

Fowler, E. G., Staudt, L. A., Greenberg, M. B., & Oppenheim, W. L. (2009). Selective Control Assessment of the Lower Extremity (SCALE): Development, validation, and interrater reliability of a clinical tool for patients with cerebral palsy. *Developmental Medicine and Child Neurology*, *51*(8), 607–614. https://doi.org/10.1111/j.1469-8749.2008.03186.x

Gage, J. R., Schwartz, M., Koop, S., & Novacheck, T. (2009). The identification and treatment of gait problems in cerebral palsy. In *The identification and treatment of gait problems in cerebral palsy*.

Goudriaan, M., Nieuwenhuys, A., Schless, S. H., Goemans, N., Molenaers, G., & Desloovere, K. (2018). A new strength assessment to evaluate the association between muscle weakness and gait pathology in children with cerebral palsy. In *PLoS ONE* (Vol. 13, Issue 1, p. e0191097). Public Library of Science. https://doi.org/10.1371/journal.pone.0191097

Killip, S., Mahfoud, Z., & Pearce, K. (2004). What is an intracluster correlation coefficient? Crucial concepts for primary care researchers. *Annals of Family Medicine*, *2*(3), 204–208. https://doi.org/10.1370/afm.141

Lloyd, R. S., Faigenbaum, A. D., Stone, M. H., Oliver, J. L., Jeffreys, I., Moody, J. A., Brewer, C., Pierce, K. C., McCambridge, T. M., Howard, R., Herrington, L., Hainline, B., & Micheli, L. J. (2014). Position statement on youth resistance training: the 2014 International Consensus. *British Journal of Sports Medicine*, *48*(7), 498–505. https://doi.org/10.1136/bjsports-2013-092952

Matthews, W. B. (1977). Aids to the examination of the peripheral nervous system. *Journal of the Neurological Sciences*, *33*(1–2), 299. https://doi.org/10.1016/0022-510x(77)90205-2

Mcdowell, B. C., Humphreys, L., Kerr, C., & Stevenson, M. (2009). *Test-retest reliability of a 1-min walk test in children with bilateral spastic cerebral palsy (BSCP)*. https://doi.org/10.1016/j.gaitpost.2008.09.010

Moreau, N. G. (2020). Muscle Performance in Children and Youth with Cerebral Palsy: Implications for Resistance Training. In *Cerebral Palsy* (pp. 2629–2640). https://doi.org/10.1007/978-3-319-74558-9_164

Noorduyn, S. G., Gorter, J. W., Verschuren, O., & Timmons, B. W. (2011). Exercise intervention programs for children and adolescents with cerebral palsy: A descriptive review of the current research. *Critical Reviews in Physical and Rehabilitation Medicine*, *23*(1–4), 31–47. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L368059013

%5Cnhttp://www.dl.begellhouse.com/journals/757fcb0219d89390,742538634df63cca,171ff51b4ce2f05e.html

Palisano, R. J., Rosenbaum, P., Bartlett, D., & Livingston, M. H. (2008). Content validity of the expanded and revised Gross Motor Function Classification System. *Developmental Medicine and Child Neurology*, *50*(10), 744–750. https://doi.org/10.1111/j.1469-8749.2008.03089.x

Park, E. Y., & Kim, W. H. (2014). Meta-analysis of the effect of strengthening interventions in individuals with cerebral palsy. *Research in Developmental Disabilities*, *35*(2), 239–249. https://doi.org/10.1016/j.ridd.2013.10.021

Pitcher, C. A., Elliott, C. M., Fausto, A., Valentine, J. P., Stannage, K., & Reid, S. L. (2015). Ultrasound Characterization of Medial Gastrocnemius Composition in Children with Spastic Cerebral Palsy. *Muscle and Nerve*, *52*(3), 397–403.

Ryan, J., Cassidy, E., Noorduyn, S., & O'Connel, N. (2017). Exercise interventions for cerebral palsy (Review). *Cochrane Database of Systematic Reviews*, *6*, 200. https://doi.org/10.1002/14651858.CD011660.pub2.www.cochranelibrary.com

Treece, G. M., Prager, R. W., Gee, A. H., & Berman, L. (1999). Fast surface and volume estimation from non-parallel cross-sections, for freehand three-dimensional ultrasound. *Medical Image Analysis*, *3*(2), 141–173. https://doi.org/https://doi.org/10.1016/S1361-8415(99)80004-8

van Tittelboom, V., Alemdaroğlu-Gürbüz, I., Hanssen, B., Plasschaert, F., Heyrman, L., Feys, H., Desloovere, K., Calders, P., & Van den Broeck, C. (2021). Reliability of functional tests of the lower limbs and core stability in children and adolescents with cerebral palsy. *European Journal of Physical and Rehabilitation Medicine*. https://doi.org/10.23736/S1973-9087.21.06627-2

Verschuren, O., Peterson, M. D., Balemans, A. C. J., & Hurvitz, E. A. (2016). Exercise and physical activity recommendations for people with cerebral palsy. *Developmental Medicine and Child Neurology*, *58*(8), 798–808. https://doi.org/10.1111/dmcn.13053

Young, H. J., Jenkins, N. T., Zhao, Q., & Mccully, K. K. (2015). Measurement of intramuscular fat by muscle echo intensity. *Muscle and Nerve*, *52*(6), 963–971. https://doi.org/10.1002/mus.24656