NCT03756571

ANALYSIS PAN

Cerebral Palsy: Ankle Foot Orthoses - Footwear Combinations

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Analysis Plan:
For both Specific Aims, our primary analysis will be an intent-to-treat analysis using outcomes collected during the parallel group RCT phase, (i.e., before TSAFO group crosses over to AFO-FC). This will be cross-sectional analysis based on linear regression models in which outcomes at primary endpoint of T1 (3-month) are the dependent variables, group indicator is the predictor of interest, with including baseline outcomes, and biomarkers of age, gender, gait pattern (equinus or crouch) and GMFCS. A secondary repeated measure analysis based on mixed effects models will also be conducted to examine the changes in outcomes across all 3 time points (T0, T1 and T2). In this analysis, group indicator will be entered as a time-varying predictor given the waitlist design (for AFO-FC group the indicators take values (0, 1, 1), whereas for TSAFO group the indicators take values (0, 0, 1)), time will be modelled as a discrete variable, and between group differences will be examined by group-by-time interactions and likelihood ratio test.

Study Design and Randomization.
A randomized waitlist trial [38] will be used to compare the AFO-FC to TSAFO (See Fig. 4). After enrollment, subjects are randomized to either wearing the AFO-FC (the intervention group) or TSAFO (waitlist group). There will be three main time points for assessment (T0, T1, T2) with the initial baseline assessment (T0) split over 2 visits. The first baseline visit includes consent, randomization, casting for orthoses (AFO-FC or TSAFO), and completion of parental report surveys (physical activity, function, satisfaction). For subjects in the intervention group, the second baseline visit includes attachment of accelerometer for 2 week assessment of community walking, fitting and tuning of new orthoses and shoes per AFO-FC algorithm, and gait analyses in barefoot and with AFO-FC. The intervention group return after two weeks of AFO-FC wear to check/adjust alignment using the VVGL, then wear the AFO-FC for three months before returning for their third assessment visit (T1). For subjects in the waitlist group, the second baseline visit includes fitting new TSAFO, attachment of accelerometer and gait analyses in barefoot and with TSAFO. They then wear

the new TSAFO for three months before returning for their third assessment visit (T1) after which they cross-over to the intervention group and undergo the same protocol as the original intervention group. The same outcome measures are administered at baseline and 3 months post fitting (T1) to assess effect of AFO-FC or TSAFO wear. At 6 months post fitting (T2), all outcomes except gait analyses are collected again to assess retention (T2).

To ensure internal validity of treatments and address reported parental concerns (See C.3. Aim #1), all orthoses will be cast, fit and tuned by a single study orthotist and PI. Cascade Orthotics, Bellingham, WA, USA, will fabricate all orthoses. Standardized shoes will be provided to minimize challenge of finding shoes for both TSAFO and AFO-FC. The PI and study orthotist will meet weekly to review quality of devices, fitting and tuning of all orthoses/shoes. A single orthotist will make all the orthoses, which will keep fabrication, (i.e. material thickness, trim lines), consistent. Consistency of AFO-FC prescription will be further facilitated by use of a published decision tree [8, 37] that the PI has experience (6 years) implementing within clinical practice at Seattle Children's Hospital. The local study team will meet monthly to review enrollment data, data collection logistics, and data quality (survey/gait lab/StepWatch). This information will then inform any adjustment to the protocol needed to troubleshoot challenges and ensure valid data collection and study completion. Per the decision tree and confirm internal validity of the AFO-FC intervention, a single video vector gait lab (VVGL) re-evaluation will occur 2 weeks post initial fitting to adjust and confirm that a "clinically optimal AFO-FC" was obtained. Optimal AFO-FC is defined as when thigh alignment in static standing is as close to vertical as active and passive hip and knee range of motion allow, the child can attain and maintain this posture spontaneously, and approximation of this alignment is observed during midstance of gait [39, 40] (Fig. 3).

Participant Characteristics.

We will enroll 30 ambulatory children with spastic diplegia CP, aged 4-9 years and Gross Motor Function Classification System (GMFCS) levels of II or III [41]. All participants will be clinically appropriate for a solid AFO based on physical exam/visual gait analysis criteria of: (1) insufficient gastrocnemius length to allow knee extension with ankle dorsiflexion of 10 degrees and an uncompromised foot arch; (2) low tone in the calf muscles with inability to control dorsiflexion during stance; (3) insufficient calf muscle strength to prevent excessive dorsiflexion in stance and create a 'quasi stiff" ankle in terminal stance that allows the heel to rise from the ground; and (4) insufficient triplanar boney stability of the foot during stance phase dorsiflexion [5, 6, 30]. Sample will be stratified by age (< 6 years or older) and GMFCS level. Only children with spasticity as their primary movement disorder and abnormal leg segment alignment during stance (crouch or equinus), will be enrolled to partially control for the heterogeneous clinical presentation found in this population. Elementary school age children are included, per ability to participate in the assessment sessions, yet limit fixed musculoskeletal

contractures often found in older children with CP. Participants who have undergone orthopedic or neurological surgery less than 6 months prior to enrollment or injection therapies (phenol, botulinum toxin) less than 3 months prior to enrollment will be excluded. Orthopedic and neurological surgeries as well as injection therapies are common interventions for children with CP in this age range and with these functional walking levels.

Outcomes Measures:
Aim #1: Gait Deviation Index (GDI) and gait speed (Aim 1) will be assessed at the Orthocare Innovations 3DGA laboratory in Edmonds, WA. At the baseline second visit (T0), gait analyses will be conducted in random order at self-selected walking speed both barefoot and with either a TSAFO or the fit/tuned AFO-FC. Three months post fitting, final gait data is collected (T1) in random order at self-selected walking speed barefoot and with the AFO-FC for the intervention group or TSAFO for the waitlist group. During 3DGA, skin-mounted retro-reflective markers are placed on the child to collect the 3D joint/segment motions and forces using an 8-camera Vicon MX system with two integrated AMTI force platforms. Consistent with best practices in motion analysis that ensures consistency of motion data, markers will be attached by the same experienced lab personnel according to the Plug In Gait model and post-processing of all gait lab data carried out by one individual. Outcome data for each limb will be summarized by averaging all trials for each walking condition (barefoot and/or TSAFO and/or AFO-FC) during each study visit (minimum of 3 trials per condition). A single number, the GDI, is derived from the deviation of the subjects' data from a normal kinematic profile dataset of kinematic features including pelvic tilt/obliquity/rotation, hip flexion/extension and abduction/adduction, knee flexion/extension, ankle dorsiflexion/plantarflexion and foot progression [13].

In order to explore specific joint kinematic changes (Aim 1) with the AFO-FC versus TSAFO that contribute to the overall GDI, we will also calculate the Gait Profile Score (GPS) and Gait Variable Score (GVS) from the GDI. Similar to the GDI, the Gait Profile Score (GPS) represents the pattern of deviation as a single number and is derived from the same individual joint/limb gait kinematics as GDI. The GPS is calculated on all gait features via the root mean square difference between the subject's data and the average of the normative data set [13]. GVS, also a single number, can only be derived from the GPS and consists of nine joint/limb gait variables for each side of the body (i.e. sagittal knee flexion midstance with an overall score for the pelvis [52].

AIM #2: The primary outcome of community walking activity will be captured with the ankle worn StepWatch (SW) accelerometer with balance quantified using the Pediatric Balance Scale. Parental report will capture physical activity with the Activity Scale for Kids – Performance version (ASKp), activity, fatigue and pain with selected items from the Patient-Reported Outcomes Measurement

Information System (PROMIS) and satisfaction with devices via the Orthotic and Prosthetic Users' Survey (OPUS). StepWatch (SW) – A pager sized accelerometer worn on the ankle, the SW. has one of the highest levels of accuracy for detecting steps across walking speeds from among commercially available monitors. SW daily stride levels for typical children and a large cohort with CP have been documented.

Power and Sample Size:
We will power this exploratory study based on our case series data (n=4, Fig. 5), published MCID for the Aim #1 primary outcomes of GDI and gait speed and published data for walking activity in CP [1, 45, 50]. A total sample size of 27 would allow 80% power to detect a 5 point GDI difference between groups with 97% power for a 7 point difference (MCID = 4.3 to 5.0) [45, 49] between TSAFO and AFO-FC. This sample size will have 83% power to detect a 0.10 m/sec difference in gait speed between groups with 95% power for a 0.15 difference (MCID=0.10 m/sec [50]) between conditions. A sample size of 27 has >99% power to detect a 2,000 strides/day treatment condition difference per StepWatch. This is based on the PI's cross-sectional StepWatch strides/day data from 134 youth with CP (GMFCS level II, n=84; level III, n=50; ages 2-14 years) with a mean difference between GMFCS levels of 1,630 strides (SD=2100) [1]. Therefore, we will enroll 30 participants to account for 10% attrition.