***Title*: Effect of Single Event Multi Level Chemoneurolysis with AbobotulinumtoxinA (Dysport®) on Energy Expenditure and Walking Efficiency in Children with Cerebral Palsy**

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1. INTRODUCTION

Cerebral palsy (CP) is a movement and postural disorder due to lesion to immature brain. Spasticity is the most common movement disorder in children with cerebral palsy (CDC) and causes difficulty with walking, musculoskeletal complications such as hip dislocation, scoliosis and joint contracture, pain and balance issues (Balaban et al., 2012). Spastic muscles are stiff and weak (Campbell & Ball, 1978). A combination of spasticity and weakness in children with CP makes them walk difficult and less efficient. Spasticity management has been very important for children with CP for activity of daily living including walking (Massin & Allington, n.d.) Using botulinum toxin A (BoNT-A) injections to control spastic lower limbs became almost first line treatment for children with CP to improve gait, range of motion and quality of life. (Ade-Hall & Moore, 2000). Several studies reported that children with CP showed higher energy expenditure during walking compared to typically developing peers. (Balaban 2007 & Rose et al 1990 Steele K et al 2017) This increase is due to combination of the mechanical inefficiencies during ambulation caused by spasticity (Reddihough et al., 2002), muscle co-contraction ((Balaban et al., 2012), limited range of motion, muscle weakness and loss of balance (Norman, 2004). Perhaps, improving coordination of walking by reducing in spasticity with BoNT-A may improve energy expenditure by improving coordination of muscle activity which is related to peak power output (Wakeling et al, 2010). Energy expenditure is an objective measure of evaluating the energy cost required for movement (Rose et al., n.d.) Generally, the oxygen consumption (VO2) is used to measure energy expenditure and one of the most significant markers of aerobic fitness and endurance (*ACSM's Advanced Exercise Physiology*, 2006). The rate of oxygen consumption (mL/kg/min) was significantly higher in the children with diplegia than in those with hemiplegia or with spina bifida or the healthy children (Rose et al., n.d.). Oxygen cost (mL/kg/m) was significantly higher, and velocity was significantly slower in all the groups with disability than in the healthy children (Duffy and Graham 2014). Balaban et al showed that botulinum toxin A injections to spastic gastric muscles decreased VO2 and gait parameters at 2-month post injections. We hypothesized that BoNT-A injections to spastic lower limbs of ambulant spastic CP decrease energy expenditure during walking. The aim of this study is to investigate the effect of spasticity management using Dysport® (AbobotulinumtoxinA) on the walking efficiency, oxygen consumption and gross motor function and gait parameters of children with CP.

2.DESIGN

This study is a single center, open label study.

We seek to recruit 15 children diagnosed with Cerebral Palsy (CP) in order to determine the efficacy of single event multi level chemoneurolysis (SEMLC) with Dysport® on energy expenditure as measured by oxygen consumption (VO2) during the 6 minute walk test.

Subject Visits:

- **Baseline**: Consent, Modified Ashworth Scale, modified Tardieu Scale, CP Quality of Life Questionnaire for Children/Adolescents, 6 minute walk with VO2 and gait analysis
- **Treatment:** SEMLC treatment

- **4 week follow-up:** Modified Ashworth Scale, modified Tardieu Scale, CP Quality of Life Questionnaire for Children/Adolescents, 6 minute walk with VO2 and gait analysis
- **12 week follow-up:** Modified Ashworth Scale, modified Tardieu Scale, CP Quality of Life Questionnaire for Children/Adolescents, 6 minute walk with VO2 and gait analysis

2.1 Participants

All subjects will be recruited from Dr. Kim's Pediatric Physical Medicine & Rehabilitation clinic. Dr. Kim will approach eligible patients and their parents in order to explain the study and to determine interest. A researcher of the study team will email and/or telephone call eligible participants on behalf of Dr. Kim and with her permission to inform the parents of the eligible participant of the study.

Inclusion Criteria:

- Age: 5-17 years. *Must be <18 prior to injection.*
- >10 kilograms at screening and injection visits
- Diagnosis of spastic diplegia OR mild- to moderate spastic quadriplegia Cerebral Palsy
- Gross Motor Function Classification System level: I, II, III
- Ability to ambulate independently without aid, equinus gait
- Absent of joint or bone deformities
- Eligible to receive SEMLC
- Cooperative and tolerant to testing procedures during clinic screening
- Presence of spasticity in one or both legs
- Be on a stable dose and regimen if on any prescribed medication/s
- Parent must have signed written informed consent and the Patient Authorization for Use and Release of Health and Research Study Information

Exclusion Criteria:

- Ankle contractures no more than -10 degrees with the knee extended
- Hemiplegia
- Wheelchair dependent
- Received Botulinum toxin within previous 4 months
- Uncontrolled epilepsy or certain types of seizures
- Fracture in the study limb within previous 12 months
- Infection or skin disorder at planned injection site
- Shortness of breath or other respiratory issues
- Uncontrolled clinically significant medical condition
- Received phenol or alcohol block in the study limb within previous 6 months
- Surgery in the study limb within previous 12 months
- Serial casting within previous 12 months
- New physiotherapy and/or orthotic regimen <1 month before study start. (physiotherapy and/or orthotic regimen will be permitted if it began >1 month before study start and maintained throughout study)

2.2 Outcome Measures

Primary Question: Does single event multi level chemoneurolysis (SEMLC) have an effect on energy expenditure and walking efficiency as measured by oxygen consumption (VO2) and gait parameters during the 6 minute walk test in 15 children diagnosed with cerebral palsy (CP)?
Hypothesis: If 15 children receive SEMLC, then energy expenditure (VO2) will decrease due to increased walking efficiency and gait parameters during the 6 minute walk test.

Secondary Question: Does SEMLC have an effect on 6 minute walking distance in 15 children diagnosed with CP?
Hypothesis: SEMLC will increase the distance walked during the 6 minute walk test.

Secondary Question: Does SEMLC have an effect on the Gross Motor Functional Classification System (GMFCS) classification in 15 children diagnosed with CP?
Hypothesis: SEMLC will decrease a child's GMFCS classification due to increased physical function.

Secondary Question: Does SEMLC have an effect on ankle muscle spasticity as measured by the Modified Ashworth Scale (MAS) and the modified Tardieu Scale?
Hypothesis: SEMLC will decrease ankle muscle spasticity and in turn improve MAS and modified Tardieu Scale scores.

Secondary Question: Does SEMLC have an effect on dynamic balance during walking in 15 children diagnosed with CP?
Hypothesis: SEMLC will increase dynamic balance during walking.

2.3 Procedures

Baseline (within 1 week prior to Dysport® treatment):

Before initiating any study procedures the informed consent will be discussed and signed with the parent(s) of the participants and the researcher will answer any questions. If capable of providing assent (>7 years old), the participant will sign the assent form. Once the consent and assent forms are discussed and signed the following assessments will be performed: demographics, height, weight, calculated body mass index (BMI), Modified Ashworth Scale (MAS), modified Tardieu Scale, range of motion of major joints (i.e., hip, knee, ankle), the Cerebral Palsy Quality of Life Questionnaire (CP QOL) for Children (9-12 years) or Adolescents (13-18 years), and the CP QOL for caregivers, 6 minute walk test (with mobile oxygen consumption), and gait analysis.

Degree of spasticity/tone in the lower limbs will be measured by the Modified Ashworth scale while the participant is relaxed and in the supine position (1). If testing a muscle that primarily flexes the hip, knee, or ankle joint the investigator will place the joint in a maximally flexed position and move the joint to a position of maximal extension over one second. If testing a muscle that primarily extends the hip, knee, or ankle joint the investigator will place the

joint in a maximally extended position and move the joint to a position of maximal flexion over one second.

The Modified Tardieu Scale will be used to assess spasticity by measuring different angles of muscle reaction in response to a passive force (2). Two angles will be measured from each major joint (i.e., hip, knee, ankle): R1, the angle in which clonus was felt during a quick passive stretch of the muscle; R2, the angle of full passive range of motion. The difference between the two angles (R2 – R1) will be recorded for each muscle group. The participant will be lying supine for all angle measurements.

Range of motion of the lower limbs (hip, knee, ankle) will be measured by passively moving the patient's joint to a point of resistance where then the joint angle will be measured by a goniometer. Hip flexion will be measured with the patient lying supine. Knee flexion and extension will be measured with the patient lying supine. Ankle dorsiflexion will be measured with the knee extended in the supine position. The Thomas Test will also be used to assess hip flexion with the patient lying in supine (3).

The CP QOL for children, adolescents, and caregivers will be used to assess quality of life and wellbeing across multiple domains of life (4). For children 4-12 years, we will give the primary caregiver version to their parent or guardian. For children 9-12 years, we will give the child self-report version. For adolescents 13-18 years, we will give the teen self-report version as well as the primary caregiver version to their parents or guardian. The sum for each domain will be calculated as well as the total sum.

Gait analysis and the 6 Minute Walk Test (6MWT) with oxygen consumption measurement (energy expenditure) will be performed in the Department of Rehab by an exercise physiologist. Children will be given at least a ten minute rest between measures.

Gait analysis will be measured with the GAITRite® mat, a commercially available instrumented mat for collection of gait data. The GAITRite system is an electronic walkway that connects to a computer, and automates the measurement of temporal (timing) and spatial (distance) gait parameters, such as cadence, step length and velocity. The standard GAITRite walkway is (5m long) and contains 13824 sensors encapsulated in a roll up mat to produce an active area 0.6 m wide and 4.25 m long. The walkway is portable, can be laid over any flat surface and requires no placement of any devices on the patient. GAITRite uses no radiation, electricity or ultrasound to measure these parameters and is therefore a safe method for evaluating walking function, even during pregnancy. The system has been validated for use in healthy children and children with movement disorders (such as cerebral palsy, and spinal muscular atrophy) (5, 6). The laboratory consists of a 10-meter walkway. The GAITRite mat is placed in the middle of the 10 meter walkway to collect data on steady state gait without the influence of gait initiation and termination. Subjects will be asked to wear the same shoes and orthoses throughout the study. A gait aid can be used during the test if the child cannot walk without it. Subjects will be asked to begin walking at a starting position located 1.5 meters from the mat and walk at their preferred typical speed until a termination position marked on the floor (1.5m from the end of the mat). Each subject will perform five trials of walking at their preferred speed. We will compute gait

velocity, step length, cadence, percent time spent in double support, foot angle, and base of support.

After at least a ten minute rest, oxygen consumption via the breath-by-breath method using a portable spirometric device (Cosmed K5; COSMED USA Inc, Concord, CA) will be determined while the participant performs the 6MWT (7). After instruction the participant will don the face mask and a 12 lead ECG will be applied. In order for the child to become comfortable with the face mask, a three minute rest period will be given while resting heart rate (HR) and oxygen consumption (VO2) is measured. After the three minute rest, the participant will begin the 6MWT while the K5 mobile device collects gas exchange variables [VO2, VCO2, respiratory exchange ratio (RER)] and HR will be monitored via the 12-lead ECG as well as cardiac rhythm. Participants will be instructed to walk at their normal walking pace as far as they can for six minutes. They will be allowed to walk with any orthoses and/or assistive devices however the same orthoses and/or devices will be used throughout the study. The participant can stop at any time if they feel dizzy or fatigued to the point of increased risk of falling. The total distance walked (meters) will be recorded at six minutes.

(Dysport® Injection/Treatment)
The procedures for Single Event Multi Level Chemoneurolysis (SEMLC) with Dysport® will mimic those currently used by Dr. Kim in the pediatric rehab clinic (8). The study drug, Dysport, will be provided by the funding source IPSEN and will be the sole abobotulinumtoxinA used in the SEMLC injection. Dysport® is currently FDA-approved for pediatric patients 2 years and older to treat lower limb spasticity (gastrocnemius and soleus). Selected dose of medication will be determined by affected muscle(s), severity of spasticity, and the patient's body weight. We will follow the recommended total Dysport dose of 10-15 units/kg per limb, not to exceed 15 units/kg for unilateral lower limb, 30 units/kg for bilateral lower limb, or a total of 1000 units, whichever is lower in a given session. The research pharmacy will be responsible for housing and preparing all Dysport® vials according to manufacturer (prescribing information sheet attached). The research pharmacy will also be responsible for study drug disposal at end of study. Electrical stimulation and/or ultrasound will be used for guidance of injection point. General anesthesia will be used to prevent pain and anxiety in adolescents if extensive multi-level injections are planned. All injection procedures will take place in the pediatric Endoscopy Suite (CHONY), and will be led by Dr. Kim (PI).

(4 Weeks Post Treatment)
All procedures during the 4 weeks post treatment will mimic those conducted during the baseline visit (i.e., Modified Ashworth Scale, Modified Tardieu Scale, range of motion, CP QOL, gait analysis, 6MWT with oxygen consumption).

(12 Weeks Post Treatment)
All procedures during the 12 weeks post treatment day 1 will mimic those conducted during the baseline day 1 visit (i.e., Modified Ashworth Scale, Modified Tardieu Scale, range of motion, CP QOL, gait analysis, 6MWT with oxygen consumption).

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