EFFECTIVE MOVEMENT CONTROL (RE) HABILITATION IN CEREBRAL PALSY: THE USE OF TRANSLINGUAL NEUROSTIMULATION (TLNS)

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ABSTRACT

PURPOSE. To investigate the acceptability, efficacy, and effect duration of translingual neurostimulation (TLNS) plus standard therapeutic exercise program (TEP) to improve motor skills in children with cerebral palsy (CP).

METHODS. Participants aged 2–17 years (n = 134) diagnosed with spastic diplegia CP with coordination and mobility symptoms were enrolled at Sestroretsk City Hospital № 40. Participants were offered one of two treatment regimens: either TEP plus TLNS with the Portable Neuromodulation Stimulator (PoNS™) – experimental arm or TEP alone (control). The treatment course continued for ten days (2 weeks, excluding two weekend days). In the experimental group and TEP, TLNS was applied twice a day, 20 minutes each during exercises, morning, and afternoon, at least 3 hours between sessions. Assessments before and after therapy courses measured spasticity, balance, and motor skills. Either treatment could be repeated several times (6–12 months between courses). All children were assessed before and after a course round of therapy using standard scales for spasticity, balance, and motor skills (Ashworth scale, Berg scale, Gross Motor Function Classification System, Functional Movement Screen). Results: Both groups of patients showed improvement; however, the improvement was significantly more significant in the experimental group across all scales, observed in all ages, and largely sustained for 6–12 months.

CONCLUSIONS. TLNS plus TEP can be considered as a novel and promising strategy to improve neurorehabilitation outcomes in children with CP, offering broad implications for the development and use of TLNS in CP.

KEYWORDS: translingual neurostimulation, cerebral palsy, neuroplasticity, balance, vestibular function, motor skills.

Introduction

Cerebral palsy (CP) induced severe, persistent motor impairment has profound social implications, and improving balance and mobility in CP, is a neurorehabilitation challenge. Altered muscle tone and impaired coordination and balance (1) cause persistent motor stereotypy, delaying motor skills development in CP. Such skills may deteriorate should secondary orthopedic complications progress, especially during the critical ages between 6–9 years (2).

Rehabilitation goals in CP change with age, and currently, no single therapy has been proven effective for all presentations. Maneuvers often include physical (PT) and occupational therapies (OT), aiming to reduce spasticity, increase movement amplitude, and develop or improve impaired function. Innovative therapeutic techniques and devices have been developed, using mechanical and robotic equipment (Lokomat®, and Armeo®, Hocoma and MOTOmed®, Reck-Technik) (3, 4), computerized exercisers, virtual reality tools (5), and specialized suits for proprioceptive system training (e. g., Adeli, Gravistat) (3). However, these interventions do not significantly impact CP outcomes (6). Muscle tone changes can induce improved limb movement quality or postural control in some. Still, benefits are short-lived, disappearing over 1–6 months, and do not result in significant motor skill development, reduced spasticity, or improved quality of life (7).

PT may promote neuroplasticity through increased synaptic strength and changed cortical maps (8), resulting in enduring functional changes (9). Combining PT with neuromodulation to encourage neuroplastic response shows promise; noninvasive neurostimulation provokes cortical excitability lasting beyond treatment periods (10) and stimulates synaptogenesis (11–13).

Neuromodulation approaches that impact different hierarchical levels of motor control or neural plasticity include functional electrical stimulation (FES), spinal cord stimulation (SCS), and several implanted and noninvasive brain stimulation approaches. FES is commonly deployed in CP (14). However, decreased muscle tone is temporary, only lasting several hours post-treatment (15).

SCS with implanted electrodes reduces spasticity in various conditions (16), including CP (17). Transcutaneous SCS has also shown promise, improving posture maintenance and walking quality, but decreased spasticity decrease was not observed (18).

Implanted deep brain stimulation (DBS) is used to treat dystonia, including adults with CP (19). Dystonia decreases by 20–24 % with DBS, but recovery and effect stabilization may take up to 1.7 years. However, DBS does not reduce spasticity, improve mobility, or improve the level of disability (20, 21). Furthermore, DBS is an invasive procedure with attendant surgical risks (infection, bleeding, anesthetic issues), side effects (dysarthria, paresthesia, loss of equilibrium). It may necessitate repeated operations due to skull growth in children under ten years old (22).

Noninvasive brain stimulation solutions are being studied with either transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS or repetitive, rTMS) (23, 24).

tDCS has been applied to children with ischemic stroke (25, 26), hyperactivity (27), autism (28), and Epilepsy (29, 30). In children with unilateral spastic diplegia, tDCS induced slight improvement in proprioception, mobility, body control, walking, and spasticity, but improvements only persisted from several weeks to several months (31, 32).

TMS has been used as a diagnostic tool to evaluate central and peripheral function to define the extent of neurological insult. An alternating electromagnetic field stimulates the cortex by inducing motor-evoked potentials, hence contraction of corresponding muscles, and changes excitation or inhibition of cortical zones. TMS is used to address headaches(33), anxiety–depressive syndrome (34), autism (35), autonomic somatoform dysfunction (36), and Tourette's syndrome (37), with many experiencing improvements (38). TMS has also been used in children to improve retarded speech development due to residual encephalopathy and attention deficit hyperactivity disorder (39). In CP, TMS decreases spasticity (40). However, the benefit was temporary, and balance and coordination were not improved.

Widespread use of noninvasive brain stimulation (TMS and tDCS), especially in pediatric patients, include side effects, such as headache, itching, nausea, fatigue, and stomach pain, for review (25) and tDCS may also cause skin irritation and redness, discomfort, and pain (41–43).

The research originating in Dr. Paul Bach-y-Rita's laboratory at the University of Wisconsin suggests that translingual neurostimulation (TLNS) can also induce neuromodulation and enhance a neuroplastic response (12, 13).

The tongue is an ideal portal for neuromodulation because the oral cavity has constant acidity (pH) and temperature. It is permanently moist, with resultant efficient electrical conductivity, requiring lower excitability thresholds than other body areas, reducing the likelihood of local complications common to other neurostimulation methods. Positive pilot and case studies in subjects with multiple sclerosis (11, 44), stroke (45), and traumatic brain injury (TBI) (46, 47) suggest TLNS may be a safe and effective method to stimulate the central nervous system (48–51). The tongue has high mechanoreceptor density, a minimum two-point discrimination threshold of 0.5–1 mm for mechanical stimulation, and 0.25–0.5 mm for electrical stimulation (52).

Two cranial nerves, 20,000–22,000 fibers of the trigeminal nerve (V), and 3,000–6,000 fibers of the facial nerve (VII) innervate the tongue's anterior surface transmitting impulses directly to brainstem structures, activating mesencephalic, sensory, and large spinal trigeminal nerve nuclei (53–55). Concurrently, the adjacent solitary tract nucleus is stimulated through a facial nerve branch. The cochlear nuclei, medulla, and upper parts of the cervical spine, up to C 2 and C 3 levels, are also directly activated (54).

The brainstem's reticular formation, locus coeruleus (blue spot), vestibular nuclei, and ventral part of the cerebellum are secondarily activated (56). The brainstem area has a large constellation of about 86 neural nuclei and structures; some regulate autonomous functions (circulation, respiration), and others are involved in sensorimotor integration. Possible secondary activation of systems regulating global neurochemical brain activity, whose nuclei are located in the brainstem (e. g., noradrenergic, dopaminergic, serotoninergic, and acetylcholinergic), may also be involved. Descending pathways regulating spinal cord motor neuron activity (trigeminal-spinal, solitary-spinal, and the three vestibulospinal pathways) directly involved in lower limb activity and walking originate from the same area.

Other noninvasive brain stimulation approaches physically stimulate selected cortical zones, whereas TLNS initiates nerve impulses originating in the tongue epithelium, activates nuclei in the brainstem and cerebellum, and generates a generated activity extend throughout the entire central nervous system. Combining TLNS with a specialized therapeutic exercise program (TEP) influences all motor activity components; central (cortical) (57, 58), subcortical (basal ganglia, cerebellum, brain stem) (59, 60), and spinal cord centers (61, 62). Therefore, multilevel neurostimulation allows natural neural activation to decrease muscle tone and facilitate sensorimotor functions, such as balance and coordination during walking (63).

Materials and methods

Study design and patient population

The PoNS™ device is approved for use in Russia to treat CP and other neurologic conditions. Children aged 2 to 17 years with spastic diplegic CP presenting to our clinic for regular follow-up participated in this study. Enrollment criteria included the child's' ability to understand and execute therapist instructions, Gross Motor Function Classification System (GMFCS) level II–IV and no seizure history. Eligible participants entered the experimental arm unless parental consent for the use of TLNS was not received; otherwise, participants entered the control group; hence this is a registry trial. Parents were informed that although the PoNS device was licensed for use in Russia, there was only limited data of its use in CP, which was explained. Participants provided written informed consent for participation in study procedures and reported study data in an

anonymized manner. The study protocol, conducted at St. Petersburg City Hospital Number 40, was approved by Ethics Committee Number 61-F3. A random subgroup of participants had a structural MRI performed before and after therapy, and these data will be the subject of future communication. This work was conducted in compliance with all local mandatory health and safety procedures.

Treatment groups

Participants formed an experimental group that received a cycle of TEP plus TLNS and a control group that received only a cycle of TEP. In both groups, TEP consisted of physiotherapy (PT) and balance training (Pablo® Tyromotion; Valedo®Motion, Hocoma) aimed at learning motor skills. Physiotherapists with experience treating CP oversaw all therapy. TEP for both groups followed the same protocols with challenges made more complicated as participants› skills developed. Each course continued for ten days (2 weeks, excluding two weekend days). In the experimental group and TEP, TLNS was applied twice a day, 20 minutes each during exercises, morning, and afternoon, at least 3 hours between sessions. For TLNS, the PoNS™ device [39] was placed on the participant's tongue while performing exercises. The PoNS device records a time of electrode contact with the tongue and characteristics of exercises undertaken, allowing for independent verification of adherence to treatment protocols. However, in this study, all therapies were delivered in the clinic with professional supervision, so adherence was not an issue. All participants in both groups were encouraged to repeat therapy cycles at 6–12-month intervals; enrolment depended on social factors such as travel and financial ability to attend.

PoNS device

The Portable Neuromodulation Stimulator (PoNS™, Helius Medical Technologies, Newtown, PA, USA) device (Figure 1) was used to deliver TLNS in this study, whose objective was to study the safety and efficacy of TLNS in combination with TEP in CP. We evaluated: a) Safety of TLNS; b) Rate of muscle tone change; and c) Combined effect of TEP and TLNS on balance performance, spasticity, and motor coordination development.

Figure 1. PoNS

During 20 minutes of stimulation, the PoNS delivers approximately 26 million impulses to the tongue's anterior surface via a paddle-shaped tab with a hexagonally patterned array of 143 gold-plated circular electrodes (1.50 mm diameter, on 2.34 mm centers). The system has an operational limit of 19 V on the tongue with a nominal 5–7 k-ohm load. The biphasic waveform is specifically designed to ensure zero net DC current to minimize the potential for tissue irritation. Prior work has demonstrated this profile to be safe (49).

The PoNS delivers triplets of 0.4–60μs wide pulses at 5 ms intervals (i.e., 200 Hz) every 20 ms (50 Hz), designed to balance the stimulus dynamic range sensation quality. While voltage and pulse timing to each electrode is internally programmed and fixed, participants may adjust pulse width (perceived stimulus intensity) with two buttons. At any time point, one electrode in each of 9 sectors of the array is delivering stimulation, while the remaining electrodes serve as the current return path to the ground.

TEP

One TEP cycle included several modalities, including three sets of exercises selected individually based on the clinical characteristics and participant's psychomotor development. The first set of exercises focused on sitting independently and keeping the body erect (Figure 2A). Initially, participants would bend and unbend their arms in a sitting position on a low chair. After mastering this action, exercises with objects (weights, ball, skittle) were added. Then, in the same position, participants performed leg flexion and extension. After becoming proficient with these exercises, they practiced various spatial orientations. For example, the participant would sit on a chair, leaning on the backrest (for added complexity, without leaning on the backrest), and fix their gaze on a lighted point ahead. The instructor would slowly rotate the chair by 5, then 10, 20, and 30 degrees to the right and left while the participant continued to look at the lighted point and remained seated on the chair.

Figure 2A. The first set of exercises

The second set of exercises focused on maintaining a standing position and controlling body position during acceleration or deceleration of rectilinear motion, as well as during rotations and deviations (Figure 2B). Training began with the participant standing with their back to a wall, feet 10 cm away from the wall, buttocks pressed to the wall, arms along the body, and back straightened.

The participant remained standing in this position as long as possible, with the instructor monitoring the correct position throughout the training. If the participant changed position and could not return to the starting position, they were given a minute of rest before continuing training. Difficulty adjustments included the position of the feet with respect to the wall or each other. The closer feet are to the wall, the harder it is for the participant to stand. Besides, the closer together one's feet are, the more difficult the exercise.

Figure 2B. The second set of exercises

Once participants mastered this position, they would stand with hands reaching out to objects while tilting forward and then returning to the wall. In this case, they would begin by standing with their backs to the wall, buttocks touching the wall. Then they would lean away from the wall with their hands resting on the instructor or the chair and return to the wall with their buttocks touching the wall. In this case, the farther the feet are placed from the wall, the more difficult it is for the patient to lean away from the wall.

The third set of exercises (Figure 2C) focused on walking with and without means of support. Learning independent movement is based on maintaining the center of gravity in the correct position and adjusting during static and dynamic exercises.

Figure 2C. The third set of exercises

Between individual sessions and therapy cycles, neither group was advised to perform specific exercises or tasks, nor did the experimental group take the PoNS home at any point.

Measures

To determine therapeutic efficacy, all participants were assessed before the first day and after the last day of treatment of each cycle according to standard scales by one investigator (TSI), a duly qualified pediatric neurologist with CP expertise, blinded to which group the participant was allocated:

(1) The Ashworth scale characterized muscle spasticity and was used to assess muscle tone. Spasticity level graded from 1 (light) to 5 (very severe) [40]. Upper (ASHH) and lower (ASHL) limbs were assessed separately.

(2) GMFCS was used to assess the level of motor development [41], with the level of development, or impairment, of motor skills graded from 1 (slight deficiency) to 5 (extreme deficiency).

(3) The Berg Balance Scale, which characterizes balance and fall risk, utilizes 14 parameters corresponding to daily childhood activities [42]. Each parameter is rated 0–4, and the sum of all tests yields a score from 1 (worst) to 56 (maximum).

(4) Motor skills development was assessed with the Functional Mobility Scale (FMS). Of motor skills, level of development, or impairment, a scale from 6, slight deficiency, or severe deficiency [43]. The movement was evaluated over variable distances: up to 5 meters (e.g., in a room, FMS 5), up to 50 meters (e.g., at school, FMS 50), and up to 500 meters (e.g., on the street in FMS 500).

For safety, an electroencephalogram (EEG) study was conducted to evaluate children with prior epileptic episodes and detect epileptiform activity, which can occur in CP in the absence of clinical Epilepsy [44]. Testing was carried out for 20 minutes using functional tests, and the presence or absence of epileptiform activity was noted. Adverse events were monitored thoroughly.

Statistical processing

Because the assessment of each participant's condition by the selected scales represents categorical or ordinal values, statistical tests for nonparametric analysis were used. A nonparametric Wilcoxon matched-pairs signed-rank test was used to compare paired values before and after therapy cycles. For comparison of unpaired samples in both groups, a matched-pairs Mann-Whitney test was selected. Statistical analysis was performed using a statistical software package (JMP 13, Statistical Discovery, SAS). Results are presented using descriptive statistical analysis.

Results

A total of 134 children (63 girls and 71 boys; mean age, 7.8 ± 0.3 years) participated in the study.

At each visit, children and parents were asked to report any adverse events. All participants using the PoNS device reported a not-unpleasant tingling sensation on the tongue, commensurate with the stimulus applied;

none withdrew from the study due to this. No significant negative side effects or device-related adverse events were detected, the PoNS device was well tolerated, and no study participants withdrew due to the technology's issues.

On EEG, occurrence or exacerbation of convulsive states in children with preexisting episodes of epileptic activity (3 participants) was not recorded.

Premature birth was noted in 84 % (112/134); 72 % (96/134) was a first birth, 20 % (27/134) a second birth, and 7 % (9/134) was the third birth, following one (47 %), two (25 %), three (10 %), four (7 %), five (6 %), or six or more (4 %) pregnancies.

Ninety-four children (43 girls and 51 boys) constituted the experimental group (TLNS with PoNS ™ and TEP), and Forty children (20 girls and 20 boys), whose parents refused TLNS, were included in the control group (TEP alone). Comparative baseline data for the experimental and control groups are shown in Table 1. Participants who did not complete an entire training course due to family logistics, other diseases, or similar were excluded, as were participants whose parents wanted their children to cross over to the experimental arm

Table 1.
Baseline data. Mean (SD) for the estimated indices by a group.

GROUP		
Metric	Experimental	Control
Number	94	40
Girls/Boys	43/51	20/20
Age	7.6 ± 0.3	7.8 ± 0.5
GMFCS	3.5 ± 0.1	3.7 ± 0.1
FMS 5	2.1 ± 0.1	1.9 ± 0.2
FMS 50	1.9 ± 0.1	1.8 ± 0.2
FMS 500	1.7 ± 0.1	1.7 ± 0.2
ASHL	3.1 ± 0.1	3.3 ± 0.1
ASHH	2.7 ± 01.	2.8 ± 01
BERG[1]	16.9 ± 1.3	11.1 ± 1.7

[1]*Only the Berg index showed a small but significan difference betweem the experimental & control groups*

All participants received standard treatment, including massage, exercise therapy, robotic mechanotherapy, and hydrotherapy. Thirty seven participants in the experimental group and 11 in the control group completed a second therapy cycle. Eight participants from the experimental group completed three cycles, and two completed four cycles.

In all tests used in this study, a statistically significant TLNS plus TEP on motor skills development, balance improvement, and limb spasticity reduction was seen compared with TEP alone.

Figure 3 shows the effects of two consecutive cycles of therapy for the control group and three consecutive therapy cycles for the experimental group on gross motor skills (GMFCS). The interval between cycles ranged from 6 to 12 months. The first standard cycle of exercise therapy in the control group (n = 40) showed a slight (– 6 %) but statistically significant decrease in the GMFCS index from 3.7 ± 0.1 to 3.4 ± 0.1 ($p < 0.01$). A repeated cycle (n = 11) showed no significant changes. In the experimental group, identical to the control in terms of baseline index values, there was a significant improvement after the first motor development cycle from 3.5 ± 0.1 to 3.0 ± 0.1 (–13 %, $p < 0.0001$), almost twice the improvement than in the control group. After a repeated cycle (n = 37), a statistically significant improvement in motor development was again observed, from 3.1 ± 0.1 to 2.8 ± 0.1 (–11 %, $p < 0.01$). After a third cycle, there was again an improvement in motor development from 2.6 ± 0.3 to 2.4 ± 0.3 (–10 %). However, the decrease was not statistically significant, possibly because of the small number of patients (n = 8) and greater variability. Only two participants completed the fourth cycle, so it would be inappropriate to draw conclusions.

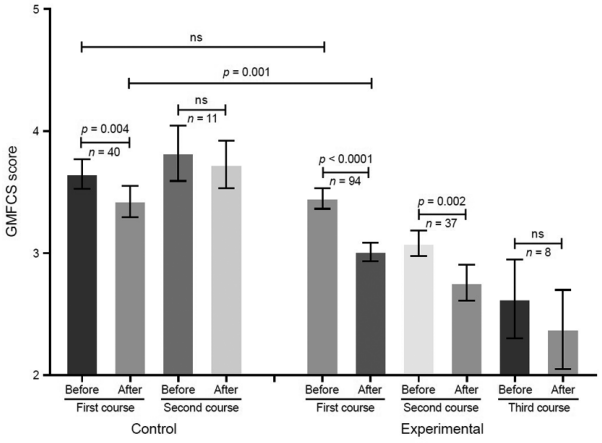


Figure 3. Changes in the level of motor disorder on the scale of gross motor skills, GMFCS

FMS data are presented numerically in Table 2 and graphically in Figure 4. As in gross motor skills, the first cycle of standard exercise therapy resulted in significant improvement in the FMS 5 index (+30 %) and FMS 50 (+17 %), though not in the FMS 500. The repetition of the standard cycle did not result in significant improvement. In the experimental group, there was a statistically significant improvement following the first therapy cycle on all three scales: FMS 5 (+59 %), FMS 50 (+51 %), and FMS 500 (+31 %). The second cycle further led to significant improvements in motor skills on all three scales: FMS 5 (+29 %), FMS 50 (+30 %), and FMS 500 (+31 %), as did the third cycle: FMS 5 (+40 %), FMS 50 (+25 %), FMS 500 (+18 %). Although the last two results were not statistically significant, due to the small number of participants and the variability of results, there was an overall positive trend in improving motor skills when using PoNS™ (Figure 4).

Table 2. FM 5, FMS 50, FMS 00 scales before and after therapy cycles

Group	FMS 5				FMS 50				FMS 500			
	Before	After	%	p	Before	After	%	p	Before	After	%	p
Control												
First cycle	1.9 ± 0.2	2.5 ± 0.2	30	***	1.8 ± 0.2	2.1 ± 0.2	17	***	1.7 ± 0.2	1.8 ± 0.2	7	NS
Second cycle	1.9 ± 0.4	2.1 ± 0.5	10	NS	1.8 ± 1.3	2.0 ± 0.5	10	NS	1.5 ± 0.3	1.7 ± 0.4	12	NS
Experimental												
First cycle	2.1 ± 0.1	3.3 ± 0.1	59	***	1.9 ± 0.1	2.8 ± 0.1	51	***	1.7 ± 0.1	2.2 ± 0.1	31	***
Second cycle	3.0 ± 0.2	3.8 ± 0.2	29	***	2.4 ± 0.2	3.2 ± 0.2	30	***	2.1 ± 0.2	2.7 ± 0.2	32	***
Third cycle	3.1 ± 0.4	4.4 ± 0.4	40	**	3.0 ± 0.4	3.8 ± 0.5	25	NS	2.8 ± 0.4	3.3 ± 0.6	18	NS

*Note: ** p < 0.01, *** p < 0.001, NS (nonsignificant) indicates absence of statistically significant difference*

Table 3: Results of the Ashworth scale

GROUP	Arm Spasticity Index, ASHH				Leg Spasticity Index, ASHL			
	Before	After	%	P	Before	After	%	p
Control								
Firstcycle	2.8 ± 0.1	2.5 ± 0.1	-11	***	3.3 ± 0.1	2.9 ± 0.1	-12	***
Secondcycle	2.8 ± 0.3	2.7 ± 0.3	-3	NS	3.3 ± 0.2	2.7 ± 0.2	-17	NS
Experimental								
Firstcycle	2.7 ± 0.1	2.2 ± 0.1	-17	***	3.1 ± 0.1	2.4 ± 0.1	-23	***
Secondcycle	2.4 ± 0.1	2.1 ± 0.1	-13	***	2.8 ± 0.1	2.3 ± 0.1	-18	***
Thirdcycle	2.3 ± 0.2	1.9 ± 0.2	-17	**	2.3 ± 0.3	1.9 ± 0.1	-17	NS

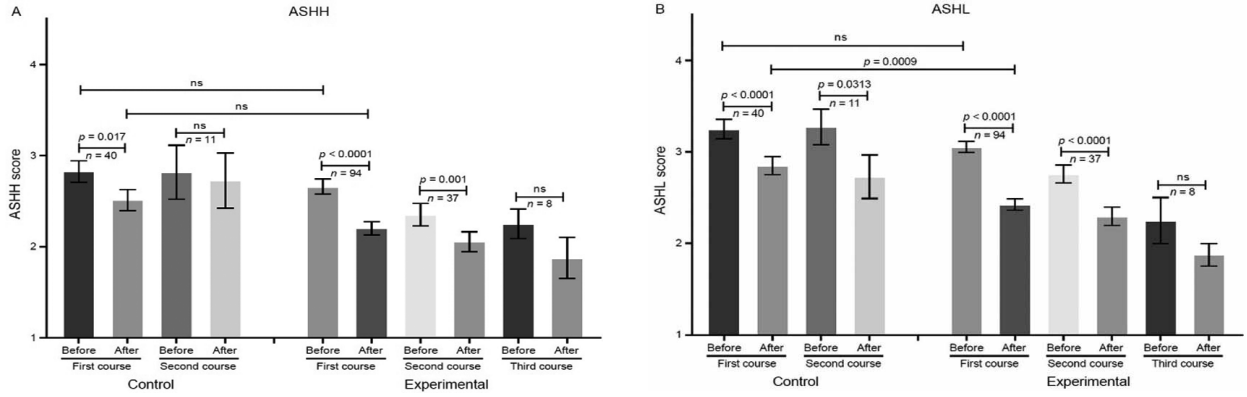
*Note: ** p < 0.01, *** p < 0.001, NS (nonsignificant) indicates absence of statistically significant differences*

A decrease in spasticity was consistent with improved mobility in both groups of patients.

The spasticity index's initial values for the arms (2.7–2.8) were slightly lower than for the legs (3.1–3.3; Figure 5, Table 3). However, spasticity tests of the arms and legs showed similar results, though spasticity reduction for the legs was slightly better. The control group showed a statistically significant decrease in the spasticity index of the arms and legs after the first cycle of therapy and a slight decrease after the second cycle. It is noteworthy that for both arms and legs, the baseline values before each cycle of therapy were the same in patients in the control group, indicating that the spasticity index returned to the initial level in the interval between cycles.

Each therapy cycle consistently reduced spasticity by 13–17 % for the hands and 17–23 % for the legs. A total decrease in the spasticity index after three consecutive cycles of therapy, compared with the first baseline measurement, reached 40–60 % or more. Even with a significant decrease in the spasticity index in the control group (by 3–11 % for the hands and 12–17 % for the legs), the experimental group's improvement was significantly better and did not return to baseline between cycles.

The number of patients rated on the Berg Balance Scale was slightly different from the other tests. Initially, 37 patients were included in the control group, 11 of whom underwent a repeated cycle, whereas 89 patients in the experimental group were tested after the first cycle



A. ASHH, Hands spasticity **B. ASHL, Legs spasticity**

Figure 5. Changes in spasticity on the Ashworth scale

of therapy, 37 after the second cycle, and seven after a third cycle. The first standard cycle of exercise therapy in the control group (n = 37) showed a statistically significant (+32 %) increase in the index from 12.1 ± 1.7 to 15.9 ± 1.8 ($p < 0.001$; Figure 6A). A repeated cycle (n = 11) also showed significant changes from 14.7 ± 2.2 to 17.4 ± 4.0 ($p < 0.05$), an improvement of 18 %. The experimental group, which had slightly better, but statistically insignificant baseline scores than the control group, showed a significant balance improvement from 16.8 ± 1.3 to 23.9 ± 1.4 (+42 %, $p < 0.001$) after the first cycle, which was better than in the control group. Following a second cycle (n = 37), there was again a statistically significant improvement in balance from 22.9 ± 2.0 to 29.8 ± 2.2 (+30 %, $p < 0.001$). After the third cycle, balance improved from 25.6 ± 5.1 to 31.1 ± 5.5 (+21 %; $p < 0.05$).

The results of two patients who completed four cycles of therapy with gaps of approximately a year are shown in Figure 6B. In both cases, improvement in balance for each therapy cycle is apparent, though the improvement dynamics were different. In one case (participant NV), the first cycle was most effective, whereas in the second case (participant SZ), the fourth cycle was most effective. It is important to note that the therapy results were maintained between cycles (up to one year) in both cases. Improvement in balance for a single therapy cycle ranged from 11 % to 63 % (participant NV) and 23 % to 44 % (participant SZ). Total balance improvement was 144 % and 229 %, respectively.

Discussion

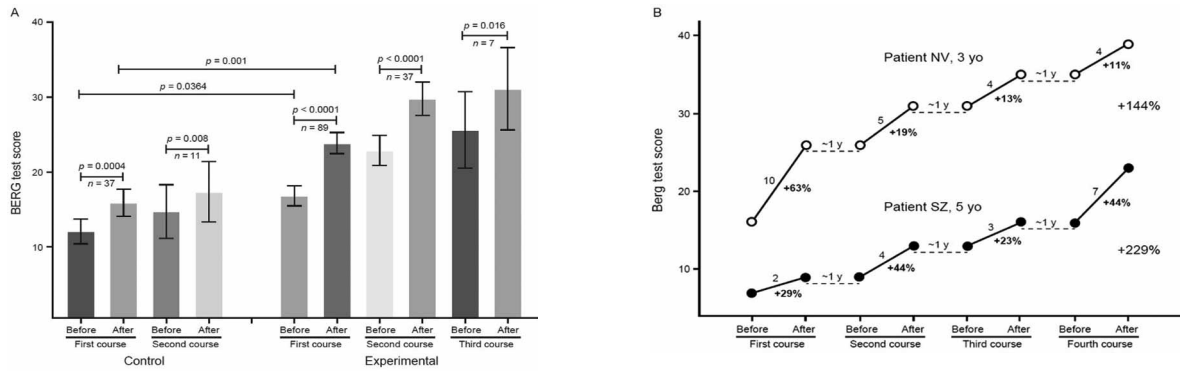
These registry data demonstrate the safety and efficacy of TLNS when combined with TEP compared to TEO alone in the treatment of CP. Control group results show TEP alone significantly improved CP's condition (Figure 3, 5, 6) but observed improvements regressed when measured before commencing subsequent therapy cycles, except for balance, which showed cumulative improvement (Figure 6A, control group).

In contrast, TEP plus TLNS showed statistically significantly improved effects. Data revealed decreased muscle tone, improved motor skills, and balance were much better than the control group after the first therapy cycle. Additionally, positive effects on spasticity, mobility, motor skills, and balance persisted or decreased slightly between therapy cycles.

Consistent demonstrable symptomatic improvement was seen with each subsequent cycle, with TLNS seemingly providing a cumulative effect to rehabilitation (Figure 6B), a response not reported with other neurostimulation modalities. The sustainability of accumulated gain is meaningful from clinical observation and quality of life perspective.

Traditional assumptions state CP reaches half their potential to develop motor skills by age five years and maximum possible development by age seven years (64) with achieved levels remaining constant or potentially declining with age. In this registry, half of the children were seven years or older (51 % in experimental, 55 % in the control group), but of interest, the younger (2–7 years) and older (8–17 years) subgroups showed similar positive trends. These results suggest that the application of TLNS-enhanced neurorehabilitation may improve the prognosis for children of any age with CP, which will be the subject of future communication.

Finally, positive and statistically significant changes in all the assessments used compared favorably to other neurostimulation methods. These effects are limited to improved muscle tone and do not extend to motor skills development, improved balance and walking, or reduced disease burden. Maintaining equilibrium in both static and dynamic tasks is an integral factor combining motor skills, reaction velocity, motion accuracy, and sensorimotor coordination. The Berg Balance Scale permits the assessment of both postural reflexes and overall coordination in balance-related tasks. In our study, we observed both a decrease in spasticity (Ashworth scale, Figure 5) and improvements in balance (Berg Balance Scale, Figure 6) and motor skills (GMFCS scale, Figure 3; FMS scale, Figure 4). Differences between the FMS individual scales are possibly caused by the exercise therapy's nature, focused primarily on



A **B**

Figure 6

A. Changes in balance according to the Berg balance scale

B. Balance performance of two patients (NV and SZ) before and after four years of training courses, approximately one year apart.

the child's behavior indoors. Moreover, after several consecutive cycles, the magnitude of changes exceeded one division of the measuring scale, indicating a possible change in impairment severity.

In the St. Petersburg 40th State Hospital, we see between 250–280 children with CP per year and have sought therapies to reliably and positively impact these patients' trajectory, thus far with no success. This study suggests that TLNS enhances physical rehabilitation effects, possibly by activating several brain areas, enhancing existing neural network efficiency, potentially increasing synaptogenesis, thereby enhancing the brain's control of motor function.

This study focused on lower extremity rehabilitation, maintaining posture and balance in static and dynamic tasks, and improving walking skills. Although rehabilitation did not include exercises targeting reducing arm spasticity or increasing mobility, significant improvements were observed in both upper and lower extremities after treatment intervention, thus suggesting a global increase in motor function with TLNS plus TEP. Successful neurorehabilitation to restore motor function or developing new motor skills using neurostimulation is achieved through combinations of specialized exercises that focus on the existing, although damaged, functional neural network. Safety and efficacy with these methods are suggested in patients with TBI (48, 63, 65), multiple sclerosis (11, 44), stroke (66), and maybe applicable to CP (67).

TLNS with the PoNS™ device is a safe, innovative, and well-tolerated enhancement to PT. Regular 20-minute TLNS sessions for two weeks in CP combined with current PT methods seemingly increased the brain's innate ability to improve motor function and promoted the formation of new motor skills.

Our findings confirm the efficacy of cranial nerve stimulation combined with targeted exercise. Perhaps a multimodal nature of CNS effects results in concurrent improvements in CP characteristics: movement coordination, balance, motor function, and reduced spasticity. These data support the notion that the human brain possesses plasticity at any age, mechanisms we are just beginning to explore.

While this study is limited by not having a randomized, blinded design or use of placebo control, the encouraging and durable results with multiple evaluations and with an excellent safety profile suggest that applications for this method in CP will doubtless be better characterized in future research such as evaluating long term outcomes, ideal treatment parameters and ideal age to initiate therapy.

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Declaration of interest

Yuri P Danilov is a co-author of several translingual stimulation patents, including PoNS™ investigational device, and co-founder/owner of Advanced Neurorehabilitation, LLC (Madison, WI), which holds the intellectual property rights to the PoNS™ technology and are exclusively licensed to Helius Medical Technologies. Yuri P Danilov is a shareholder in Helius Medical Technologies, Inc., manufacturer of the PoNS device, and a consultant to this company. TSI, VEK, GAI, AMS, APS, and SGS have nothing to disclose. Dr. Jonathan M Sackier serves as Chief Medical Officer of Helius Medical Technologies, receives a salary and stock options, and is a shareholder.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, T. S. Ignatova. The data are not publicly available due to the ethics committee's decisions and the internal policy of City Hospital Number 40.

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