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Original Article

Effectiveness of electrical stimulation after administration of botulinum toxin in children with spastic diplegic cerebral palsy: A prospective, randomized clinical study

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ABSTRACT

Objectives: The aim of the study was to investigate the effectiveness of electrical stimulation to agonist muscles after injection of Botulinum toxin A (BTX-A) in children with spastic diplegic cerebral palsy (SDCP).

Patients and methods: Between October 2009 and October 2010, 38 patients with SDCP (19 males, 19 females; mean age 6.3 years; range, 4 to 10 years) were included. The patients were able to walk independently or with minimal assistance by foot equine and had spasticity in the calf muscles between Grades 1+ and 3 according to the Modified Ashworth Scale (MAS). The patients received either BTX-A injection + electrical stimulation (Group 1, n=19) or BTX-A injection alone (Group 2, n=19). All patients were evaluated using the MAS, Penn Spasm Frequency Scale (PSFS), Gross Motor Function Measure-88 (GMFM-88) (Dimensions D and E), and walking velocity.

Results: A decrease in spasticity was evident for the right, left, and bilateral lower extremities for both groups ($p<0.05$). There were no statistically significant differences in the MAS, PSFS, GMFM-88 (Dimensions D and E), and walking velocity between the groups.

Conclusion: Our study results showed that both patient groups benefited from the treatment and the administration of electrical stimulation to the gastrocnemius motor points produced no additional benefit for patients with SDCP.

Keywords: Botulinum toxin, cerebral palsy, electrical stimulation, spasticity.

Cerebral palsy (CP) describes a group of disorders concerning the impaired development of movement and posture, causing activity limitation. This physical disability is a consequence of non-progressive disturbances which occur in the developing fetal or infant brain.[1] Spastic CP is the most common type which accounts for 75% of all cases.[2,3]

Spasticity can lead to muscle stiffness, functional impairment, and atrophy. If left untreated, it can progress to muscle fibrosis, contractures, and subsequent musculoskeletal deformities.[3]

Botulinum toxin injection is one of the most effective methods for treating focal spasticity and is also used to treat specific muscle problems in generalized spasticity and provide functional improvement.[4,5] Botulinum toxin inhibits the release of acetylcholine at the neuromuscular junction, and the therapeutic effect sustains up to three to four months and repeated injections may be required in most cases. The treatment, however, increases the risk of antibody formation.[6,7] To reduce the number of repeated injections, and to decrease the risk of antibody formation and medical costs, treatment modalities which enhance the effect of botulinum toxin are required.[7]

One of the treatment modalities which attempts to achieve the aforementioned goals is through the application of electrical stimulation to the botulinum toxin-injected muscle.[7-15] Peripherally, electrical

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stimulation acts to strengthen muscles, reduce spasticity of the antagonist muscle, reduce spasticity of the stimulated muscle, reduce co-contraction, and create soft-tissue changes which allow an increased range of motion. Centrally, stimulation enhances reorganization in the motor regions of the brain through an effect known as plasticity.[16] Nerve stimulation reduces the time required for paralysis to develop. Previous experimental studies have demonstrated that this relationship must be closely dependent upon the nerve-ending activity.[8]

To date, previous studies have usually included adults, while there are only a few studies in the literature investigating the effects of botulinum toxin injection plus electrical stimulation in patients with CP.[7,14,15] The aim of the current study was, therefore, to investigate the effectiveness of electrical stimulation applied to the agonist muscles after the administration of Botulinum toxin A (BTX-A) in children with spastic diplegic CP (SDCP).

PATIENTS AND METHODS

Participants

In this prospective, randomized clinical study, a total of 132 patients with SDCP aged between 4 and 10 years old were screened. Between October 2009 and October 2010 patients who were able to walk independently or with minimal assistance by foot equine and had spasticity in the calf muscles between Grades 1+ and 3 according to the Modified Ashworth Scale (MAS) were recruited. Patients who had previous orthopedic surgery related with the BTX-A injection area, had fixed contracture of lower extremity joints, systemic health problems, severe hamstring spasticity, BTX-A injection and/or electrical stimulation within the last six months or had a history of botulinum toxin intolerance were excluded from the study. Ninety-two patients were not eligible for the study (37 had hamstring spasticity, 14 had a surgical procedure, 12 received botulinum toxin injections within the last six months, 21 had contracture, five had electrical stimulation within the last six months, and three refused to participate in the study). Forty patients were registered for the study. Due to the loss of two patients (one in each group), however, 38 children with SDCP (19 males, 19 females; mean age 6.3 years; range, 4 to 10 years) were completed the study. A written informed consent was obtained from the primary caregiver of each patients. The study protocol was approved by the Cukurova University Faculty of Medicine Ethics Committee (2009-107/16). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study design and procedures

The patients were randomized into two groups by flipping a coin to receive either BTX-A + electrical stimulation therapy (Group 1, n=20) or BTX-A injection alone (Group 2, n=20). Both patient groups received BTX-A injections at the site of the gastrocnemius and soleus (calf) muscles and home-based exercise programs were recommended. Electrical stimulation was applied to the gastrocnemius muscle in Group 1.

Botulinum toxin-A 100 IU injection (100 IU vial, Allergan, UK) was administered to all children who participated in the study. The body weights of the patients were measured. Total dose administered to each patient (body weight-dependent) was 10 IU/kg. Each vial was diluted with 2 mL of 0.9% saline. The BTX-A was injected to the soleus and gastrocnemius muscles of both lower extremities in prone position using a 26-gauge brown needle without electromyographic guidance. The calf muscle was divided into four quadrants. The centers of upper and lower quadrants were identified as the motor points of the medial and lateral gastrocnemius muscles and deep point at the central calf were identified as the motor point for soleus. Finally, four points for medial and lateral gastrocnemius muscles and one point for soleus muscle were injected with BTX-A. Total patient dose was 10 IU/kg and dose for each injection site was 2 IU/kg BTX-A.[17] All injections were done by a single physician. Sedation was not used. Five percent local lidocaine cream was applied to the site of injection one hour before the procedure. Sterile conditions were prepared before the injection was administered. After the injection procedure, cold pack was applied locally for 10 min.

In Group 1, electrical stimulation was applied to the gastrocnemius muscle. Electrical stimulation started on the same day immediately after BTX-A injection was administered, and was performed once a day, for 20 min, for 10 days. Surface electrodes were positioned at the gastrocnemius motor points. A two-channel Intelect 2777 model Mobile device (Chattanooga Group, Hixson, TN, USA) was used for stimulation. Stimulation intensity was adjusted to a level sufficient to observe minimal gastrocnemius muscle twitching and increased according to a tolerance level which would not disturb the patient (7.5- 22 mA) (frequency: 40 pulse/sec, cycle duration: constant 10/20, phase duration: 350 μsec, increasing 0.5 sec, constant current). Electrical stimulation was not performed in patients in Group 2. After the injection, a home-based exercise program was instructed to both groups by

Table 1. Demographic features and GMFCS levels of the patients

	Group 1 (n=19)		Group 2 (n=19)		
	n	Mean±SD	n	Mean±SD	*p*
Age (year)		6.1±2.2		6.5±2.1	0.552
Gender*					0.330
Female	11		8		
Male	8		11		
BMI (kg/m^2)†		14.8±1.8		14.5±1.9	0.452
GMFCS level 1	5		4		
GMFCS level 2	5		4		
GMFCS level 3	9		11		

GMFCS: Gross Motor Function Classification System; SD: Standard deviation. BMI: Body Mass Index; * Chi-square test; † Mann-Whitney U-test.

the same physician. Exercise protocol consisted of calf stretching, ankle dorsiflexor muscle strengthening, and walking exercises.

Demographic features of the patients including age, gender, and Body Mass Index were recorded. The patients were further classified using the Gross Motor Function Classification System (GMFCS) (Table 1). The patients were evaluated by another physician. Follow-up visits were performed at baseline (pre-treatment), at two weeks and at three months after the injection (post-treatment). The primary endpoint of the study was the reduction of lower extremity spasticity as assessed by the MAS scores.[18] The secondary outcome measures included

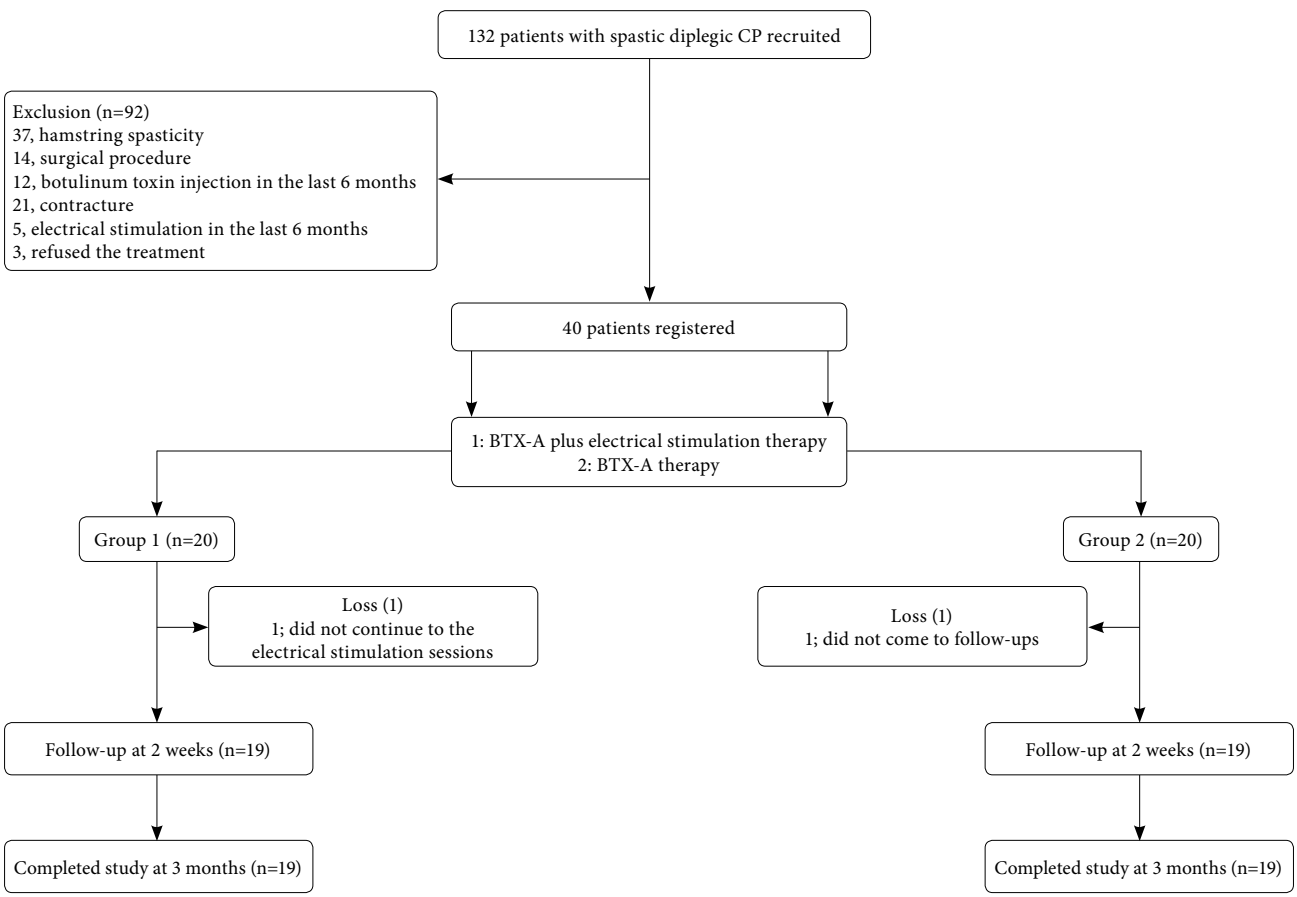

Figure 1. Study flow chart.

Table 2. Intra-group comparison of lower extremity spasticity

	Group 1 (n=19)		Group 2 (n=19)	
	Median	Min-Max	Median	Min-Max
RMAS				
Pre-treatment (1)	3	1.5-3	2	1.5-3
Week 2 (2)	0	0-1.5	1	0-1.5
Month 3 (3)	1	0-3	1	0-3
p*	<0.001		<0.001	
p_{1-2}†	<0.001		<0.001	
p_{1-3}†	<0.001		<0.001	
p_{2-3}†	0.008		0.007	
LMAS				
Pre-treatment (1)	2	1.5-3	2	1.5-3
Week 2 (2)	0	0-2	0	0-1.5
Month 3 (3)	1	0-3	1	0-3
p*	<0.001		<0.001	
p_{1-2}†	<0.001		<0.001	
p_{1-3}†	<0.001		0.001	
p_{2-3}†	0.020		0.004	

	Group 1 (n=38)		Group 2 (n=38)	
BMAS	Median	Min-Max	Median	Min-Max
Pre-treatment (1)	2	1.5-3	2	1.5-3
Week 2 (2)	0	0-2	0.5	0-1.5
Month 3 (3)	1	0-3	1	0-3
p*	0.001		0.001	

RMAS: Right lower extremity Modified Ashworth Scale; LMAS: Left lower extremity Modified Ashworth Scale; BMAS: Bilateral lower extremity Modified Ashworth Scale; p_{1-2}: Pre-treatment and the second week post-injection; p_{1-3}: Pre-treatment and the third month post-injection; p_{2-3}: Second week post-injection and third month post-injection; Note: Values are given as median (min-max); * Friedman test; † Wilcoxon test.

Penn Spasm Frequency Scale (PSFS),[18] Gross Motor Function Measure-88 (GMFM-88) (Dimensions D [standing] and E [walking, running, jumping]),[19] and walking velocity scores.[20] Walking velocity was assessed by measuring the distance covered during a fast one-min walk test. The distance walked as fast as possible in one minute was measured in meters (m). This tool is an effective method used to evaluate the functional abilities of children with CP.[20]

Statistical analysis

Statistical analysis was performed using the PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was used to compare the variables which did not represent normal distribution between the two groups. Categorical measurements were expressed in number and percentage, while continuous measurements were expressed in mean and standard deviation (SD), or median (min-max) values, where applicable. The chi-square test was used for the intergroup comparison of categorical measurements. The Friedman test was used to compare the results generated through the pre-treatment, second-week and third-month results. In case of statistical significance, the Wilcoxon test was performed to investigate the pairwise differences between two measurement times. Data distribution was tested using the Shapiro Wilk normality test and non-parametric methods were used accordingly. A p value of <0.05 was considered statistically significant.

RESULTS

In this prospective, randomized clinical study, one patient from Group 1, who was unable to complete the electrical stimulation sessions, and one patient from Group 2, who did not attend to the follow-up visits, were not included in the statistical analysis. The study was completed with the results collected from 38 patients, that is, 19 patients from each group, which were followed on a regular basis for three months. The study flow chart is shown in Figure 1.

Table 3. Inter-group comparison of lower extremity spasticity

	Group 1 (n=19)		Group 2 (n=19)		
BMAS	n	%	n	%	*p*
Pre-treatment					
0	0	0.0	0	0.0	
1	0	0.0	0	0.0	
1+	6	15.8	4	10.5	0.376
2	14	36.8	20	52.6	
3	18	47.4	14	36.8	
Week 2					
0	20	52.6	19	50.0	
1	10	26.3	15	39.5	
1+	6	15.8	4	10.5	0.331
2	2	5.3	0	0.0	
3					
Month 3					
0	14	36.8	12	31.6	
1	12	31.6	10	26.3	
1+	3	7.9	4	10.5	0.883
2	5	13.2	8	21.1	
3	4	10.5	4	10.5	

BMAS: Bilateral lower extremity Modified Ashworth Scale; Chi-square test.

There was no statistically significant difference in the age, gender, and Body Mass Index between the groups (Table 1).

According to the MAS scores, a decrease in spasticity was evident for the right, left, and bilateral lower extremities for both groups ($p<0.05$). However, there was no statistically significant difference between the two groups (Tables 2 and 3).

Improvement in the pre-treatment vs. two-week, pre-treatment vs. three-month, and two-week vs.

Table 4. Comparison of GMFM dimensions D and E (intra- and inter-group analysis)

	Group 1		Group 2		
	Median	Min-Max	Median	Min-Max	*p**‡
GMFM D					
Pre-treatment (1)	38.5	7.7-100	35.9	2.6-94.9	
Week 2 (2)	53.8	7.7-100	61.5	2.6-94.9	
Month 3 (3)	61.5	7.7-100	51.3	2.6-97.4	
pΔ	<0.001		0.002		0.528
p_{1-2}†	0.001		0.008		
p_{1-3}†	<0.001		0.001		
p_{2-3}†	0.041		0.239		
GMFM E					
Pre-treatment (1)	29.2	9.7-98.6			
Week 2 (2)	37.5	11.1-98.6	18.1	6.9-98.6	
Month 3 (3)	47.2	12.5-98.6	37.5	8.3-98.6	
pΔ	0.001		40.3	6.9-98.6	0.535
p_{1-2}†	0.003		0.019		
p_{1-3}†	0.001		0.005		
p_{2-3}†	0.007		0.007		

GMFM D: Gross Motor Function Measure Dimension D; GMFM E: Gross Motor Function Measure Dimension E; *p: Difference between the groups; p: Difference within the groups over time; p_{1-2}: Pre-treatment and the second week post-injection; p_{1-3}: Pre-treatment and the third month post-injection; p_{2-3}: Second week post-injection and third month post-injection; Δ Friedman test; † Wilcoxon test; ‡ Mann-Whitney U-test.

three-month post-injection GMFM-88 Dimension D scores was prominent in Group 1. In Group 2, there was a significant improvement in the pre-treatment vs. two-week and pre-treatment vs. three-month post-injection GMFM-88 Dimension D scores. However, there was no significant difference in the two-week post-injection scores, compared to the three-month post-injection values. Improvement in the GMFM-88 Dimension E was statistically significant for both groups. There were no statistically significant differences between the two groups for both GMFM-88 Dimensions D and E (Table 4).

In addition, there were statistically significant differences in the PSFS scores at pre-treatment and two-week measurements in both groups (Group 1; $p<0.05$, Group 2; $p<0.05$). However, decrease in the spasm frequency was significant for only Group 1 at two weeks and at three months (Group 1; $p<0.05$). There were no statistically significant differences in the pre-treatment and three-month PSFS scores between the two groups.

Furthermore, we observed no significant improvement in the pre-treatment and two-week measurements of walking velocities in both groups. Improvements in walking velocities at three months, compared to pre-treatment values, and at three months compared to two-week values, were prominent for both groups (Group 1; $p<0.05$, Group 2; $p<0.05$). However, there were no statistically significant differences in the walking velocities between the two groups.

There were no unintended effects or harms in any treatment group during the study period.

DISCUSSION

In the present study, we investigated the effect of electrical stimulation applied to the agonist muscles which were already treated with BTX-A in children with SDCP. However, we observed no additional effect of electrical stimulation to the gastrocnemius muscle after BTX-A injection which was administered to the gastrocnemius and soleus muscles in this patient population.

The main goal of spasticity treatment is to maximize active function, ease care, and prevent associated secondary problems such as pain, subluxation, or contracture. Botulinum toxin is an appropriate agent for the treatment of focal spasticity.[4]

The botulinum neurotoxin is immunogenic and repeated exposure can lead to immunoresistance.[4] If the effect of botulinum toxin can be augmented and extended, repetitive injections, pain after injection, antibody formation, and medical costs would be reduced.[7-15]Animal studies, to date, have been performed to investigate a modality to achieve this goal.

The lytic step of internalization of botulinum toxin is nerve activity-dependent.[10] In a study by Hughes and Whaler[8] with a rat phrenic nerve-diaphragm preparation, nerve stimulation was found to reduce the time required for paralysis to develop with BTX-A. Black and Dolly[9] found that nerve stimulation accelerated endocytosis and this could explain the increased uptake (by 50%) of botulinum toxin molecules bound to the presynaptic membrane after such treatment. The results obtained from animal models have paved the way for human studies.

In their study, Eleopra et al.[21] used normal human muscles and applied electrical stimulation for an extended period of time, which is difficult to compare with studies using spastic muscles. In a series of studies, Hesse et al.[22-24] demonstrated that short-term electrical stimulation applied to both agonist and antagonist muscles enhanced the effectiveness of botulinum toxin in the treatment of lower and upper extremity spasticity in adult patients with stroke. This result suggested that the degree of motor activity was an important factor for the potency of the neurolytic agent.[23] In our study, we applied electrical stimulation only to the injected muscles, as in other studies involving children with CP.[7,14,15]

Furthermore, studies on adult spasticity have demonstrated that administration of electrical stimulation to the agonist muscles after botulinum toxin injection is effective.[11-13] However, there is a limited number of studies regarding the efficacy of electrical stimulation to the agonist muscles after botulinum toxin injection for CP patients.[7,14,15] In the study by Kang et al.,[7] Rha et al.,[14] and Detrembleur et al.[15] electrical stimulation was applied in different duration. Similar to the present study, all these studies including children showed that BTX-A + electrical stimulation combination was not superior to BTX-A therapy alone in terms of reduction of spasticity.[7,14,15] In their study, Kang et al.[7] concluded that electrical stimulation could be applied more frequently and for a longer period of time in adult patients, compared to pediatric patients. This finding can explain why stroke patients benefit from the treatment, while CP children do not. Wright et al.[25] also concluded that treatment effects were observed, when neuromuscular electrical

stimulation was applied for 30 to 60 min per day for at least six to eight weeks. The authors concluded that long duration of electrical stimulation made it inconvenient for the children. Therefore, the efficacy of the treatment decreases in CP patients. In our study, electrical stimulation was performed for 20 min a day, for 10 days, which was less than the recommended protocol. This could explain the inadequate effect of electrical stimulation on spasticity after BTX-A injection in our study group.

In the present study, we used MAS, as in previous studies[7,14,15] with the PSFS and walking velocity. In addition, the GMFM-88 was administered to evaluate the motor function quantitatively.[26] Our results showed no significant differences in spasticity, walking velocity, spasm frequency, and GMFM-88 Dimension D and Dimension E scores between the two study groups. However, when the GMFM-88 Dimension D was assessed at two weeks and three months after the injection, there was an improvement in Group 1, while no improvement was observed in Group 2.

Reduction in the PSFS scores was also significant in both groups during pre-treatment and at two weeks after the injection. A statistically significant reduction was seen only in Group 1 after injection, which appears to be a consequence of electrical stimulation. To the best of our knowledge, this study is the first to use the PSFS in the evaluation of SDCP patients, we are unable to make a comparison with previous studies.

On the other hand, an unexpected finding is that there was no significant difference in the walking velocity during the pre-treatment period and at two weeks after the injection in both groups. However, when we compared the two-week and three-month values, and pre-treatment and three-month values, it became evident that walking velocity was improved in both groups. The lack of an increment in the walking velocity in both groups within the first two weeks following BTX-A injection can be attributed to the relaxation of the muscles, which makes the patient unable to adapt to a walking pattern in a short period of time.

Although the treatment plan applied in the current study differed from the studies of Kang et al.,[7] Rha et al.,[14] and Detrembleur et al.,[15] the limitations were similar including the use of a small sample size, differences in the period of time of application, and the amount of the electrical stimulation due to the difficulty of application in children and, difficulty in homogenizing the patient groups.

In a recent review evaluating the evidence of adjunct therapies to botulinum toxin injections have shown that low-frequency electrical stimulation may be better than high-frequency electrical stimulation and immediate electrical stimulation may be better than a delayed application. It has been also suggested that electrical stimulation of antagonist muscles in addition to the muscle areas injected with botulinum toxin improves the decrement of spasticity, which provides a rationale for further researches.[27]

Nonetheless, there are some limitations to this study. First, we were unable to evaluate patients with instrumented gait analysis system. Second, the patient compliance to the home-based exercise program in the treatment plan was unable to be evaluated well. Third, electrical stimulation was applied to only one of the BTX-A-injected muscle groups, which was gastrocnemius. However, in previous studies using this method, electrical stimulation was only administered to the gastrocnemius motor points, as the efficacy of electrical stimulation to the soleus with surface electrodes is not sufficient. Finally, to standardize the study groups, we employed strict inclusion and exclusion criteria which limited the number of patients enrolled in our study. We recommend further studies with a larger sample size with different patient groups and different doses of electrical stimulation and botulinum toxin to eliminate the controversy in the literature and to provide further insight into this area of study.

In conclusion, both BTX-A injection alone and BTX-A injection treatment combined with electrical stimulation to the agonist muscles can reduce spasticity in children with SDCP. There is no additional benefit of electrical stimulation to the gastrocnemius muscle following the BTX-A injection for children with SDCP.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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