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Full Length Research Paper

Efficacy of Multilevel Botox A Injection in Hemiplegic and Diplegic Spastic Cerebral Palsy: A Clinical and Neurophysiological study

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Spasticity in cerebral palsy places obstacles in the path to achieving the rehabilitation goals. Aiming to detect favorable outcomes of multilevel Botox A injection in spastic (cerebral palsy) CP children at a single session from clinical and electrophysiological aspects and to localize dependable factors for those outcomes. Twenty two spastic CP patients with lower limbs spasticity were enrolled. All patients were assessed by modified Ashworth scale (MAS), Timed 10 meter walk (TMW), Pain scale, knee and ankle ROM. Also F wave, and H reflex with F/M and H/M amplitudes and gastrocnemius (Gas) surface EMG (SEMG) for interference pattern (IP) recording. Multilevel Botox injection of Gas, Soleus, Hamstring (Ham), and Tibialis posterior muscles was done in single session. Reassessment at 1, and 6 months. Fourteen patients were diplegic and 8 were hemiplegic, 12 males and 10 females. There was significant increase in knee and ankle ROM ($P < 0.01$) at 1 and 6 months post injection. MAS, TMW and Pain scale, F/M and H/M amplitude were significantly reduced, and significant improvement of IP one month after injection which persist till the end of study. A significant negative correlation existed between MAS of (Gas Sol and Ham) at 6 month and baseline ROM ankle and knee ($P < 0.05$) and between MAS Gas and interference pattern ($P = 0.04$). ROM knee, amplitude of H/M and F/M were dependable factors for improved TMW after 6 months (TMW2) as a secondary outcome at the end point of the study. Multilevel Botox A injection reduces spasticity, and improves the short and long term outcomes. Both clinical (ROM, TMW) and neurophysiological measures (F/M, H/M, SEMG) were useful assessment tools for monitoring response to treatment.

Keywords: Cerebral palsy, spasticity, Botox A injection, Ashworth score, F wave, H reflex

INTRODUCTION

Spasticity in children with CP is a serious problem that places obstacles in the path to achieving the rehabilitation goal (Camargo et al., 2009). Spasticity is a neurological impairment that is believed to contribute not only to a loss of function but also to the development of

joint contractures and pain. *Spasticity* is defined as "disordered sensorimotor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles (Barnes, 2001).

The assessment of spasticity in clinical practice usually is accomplished with descriptive scales for evaluating the resistance to passive movement at ordinal level of measurement; one of the most frequently used scales is the Modified Ashworth Scale (MAS) (Platz et al., 2005).

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The clinical assessment of spasticity depends on descriptive scales as MAS, Pain rating verbal Scale (Wong et al., 2001) and Gross Motor Function Measure, however these may not be sufficiently sensitive to accurately detect improvements (Sohn et al., 2011). H reflex recording reflects the impact of UMN on the stretch reflex, while F waves increase in amplitude in spasticity. When relating Absolut F wave /M wave amplitudes, values of $>5\%$ are common in upper motor neuron diseases. Surface Electromyography (SEMG) identifies the presence of abnormal muscle activity. Recordings from specific muscles at rest with passive stretch give information about the resting state of the muscle and the stretch reflexes (Sohn et al., 2011). SEMG also is beneficial in recording muscle activity during maximum volition which reflects the functional improvement obtained from therapy (Albani et al., 2010).

Botulinum toxin A (BoNT/A), a practical neuromuscular blocking agent that causes a clinical reduction in spasticity in working muscles, appears to have a beneficial effect on the natural history of CP patients with equinus deformity (Bakheit, 2004). Studies reported that an Ashworth scale, gross motor function measure scores, and non independent ambulatory status which were predictive for a favorable response to botulinum toxin A injections and can guide patient selection and expectations of treatment outcome (Koman et al., 2000).

Aim of the Work

The aim of this study is to detect favorable outcomes of multilevel Botox A injection in spastic CP children at a single session from clinical and neurophysiological aspects and to localize dependable factors for those outcomes.

PATIENTS AND METHODS

This was a retrospective study, that enrolled 22 spastic cerebral palsy patients with predominantly lower limbs spasticity who attended the outpatient clinic of Physical Medicine, Rheumatology and Rehabilitation outpatient clinic of Ain Shams University hospitals.

Inclusion criteria were:

- 1- Children between 5-18 years.
- 2- Patients with correctable deformities with poor response to physiotherapy.
- 3- Patients who can walk with or without assistance.
- 4- Patients taking part in rehabilitation programs.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki for human subjects and the study was approved by the ethics committee of the faculty of Medicine, Ain Shams University. All parents' children gave us their written

informed consent before enrolment.

Patients who had spasticity predominantly in their upper extremities, fixed contractures in hip, knee and ankle; or a history of previous surgery or application of intrathecal baclofen, patients who were previously received one injection session and those with severe visual or cognitive deficit were excluded from this study.

Identification of target muscles was made after comprehensive assessment, including full history taking and thorough clinical musculoskeletal examination, with emphasis on passive and active range of motion of joints affected by spastic muscles (knee flexors and ankle flexors and invertors) by goniometer Flexion deformity was expressed in minus degree which presented extension lag. (MAS) was scored and TMW (seconds) was measured to assess changes in walking function. Pain was rated by the parents with a 5- point verbal descriptor scale: 1= no pain, 2= mild pain, 3 = moderate pain, 4= severe pain, or 5= pain could not be worse. Neurophysiological assessment by F wave, H reflex with estimation of F/M and H/M amplitude ratio. Surface EMG of spastic muscles for interference pattern evaluation were done in hemiplegic side in hemiplegic patients, and on both sides in diplegic patients.

Electrophysiological assessment was conducted at the Physical Medicine, Rheumatology and Rehabilitation Department, Ain Shams University Hospitals using Toennies Neuroscreen Plus made by Toennies of Germany. Nerve conduction studies were analyzed as motor evoked potential M response, F wave and H reflex amplitudes to get F/M and H/M amplitude using a sweep speed of 5ms/division and a gain of 4mV. Also surface EMG results were analyzed as activity level in maximum volition (ms/s).

We recorded the electromyographic activity obtained from the gastrocnemius muscle. The silver chloride active electrode was placed over the muscle belly, and the reference electrode was placed along the tendon. The ground electrode was placed over the ankle joint. The raw EMG signals were sampled at 1500 Hz and fully rectified and amplified with a bandpass filter (10-5000 Hz). The electromyographic activity was integrated using a A/D converter . Through the above procedure, we recorded the integrated electromyographic activity for the interference pattern (Fattal-Valevski et al., 2002).

Target muscles clinically thought to be responsible for the problem were initially sampled with needle EMG.

The injections were administered using a multilevel approach at a single injection session. The various muscle groups that were injected in each session were the gastrocnemius, soleus, medial and lateral hamstring and tibialis posterior muscles. Botulinum type A (Allergan, USA) toxin dose ranged from 3-6 U/Kg for large muscle of lower limb, 50 U per injection point, and maximum of 200-300U per session. The total muscle dose was divided between 2-4 injection sites, depending on muscle size. Injection was guided by electric

Table 1. Descriptive data of the patients.

Data	Mean \pm SD	Range
Age(ys)	9.60 \pm 4.62	5-18
Weight(kg)	32.30 \pm 12.30	21-60
Duration since injury(ys)	9.30 \pm 4.08	5-15
Dose of Botox(U)	183.3 \pm 100	30- 300
ROM A	-3 \pm 16.01	-20 – 25
ROM K	-20 \pm 11.92	-40 – 0
MASGast	2.55 \pm 0.89	1-4
MAS Sol	2.45 \pm 0.89	1- 4
MASHam	2.90 \pm 0.79	1-4
MAS TP	1.55 \pm 0.60	1- 3
Pain score	1.08 \pm 1.00	0- 3
TMW (sec)	46.67 \pm 17.23	20- 70
H/M	28.77 \pm 21.18	3- 66
F/M	47.55 \pm 25.49	13- 100
IP (GAS)(ms/s)	61.85 \pm 71.44	20—348

ROM A: range of motion ankle, ROM K: range of motion knee, MASGast: modified Ashworth score gastrocnemius m, MAS Sol: modified Ashworth score soleusm, Ham: hamstring, TP: tibialis posterior, TMW: 10 meter walk in seconds, IP (GAS): interference pattern of gastrocnemius.

stimulation apparatus for the exact identification of target muscles and motor points (Kim et al., 2005; Graham et al., 2000).

All the patients underwent regular physiotherapy sessions; before the BTX-A injections; which were resumed 2 days post Botox A injection in the form of 5 days a week for the next 4 weeks then 3 days a week continued for additional 2 months.

Ankle foot orthosis and night splints were prescribed. The Primary outcome was improvement in studied parameters (MAS, ROM, pain score, TMW, H/M, F/M and IP) post injection at two time interval of the study (1 month, 6 months). The secondary outcomes were dependable factors for improved TMW2 as functional performance after 6 months.

Statistical analysis

IBM SPSS statistics (V. 22.0, IBM Corp., USA, 2013) was used for data analysis. The distribution of all the data was tested. Data were expressed as Mean \pm SD for quantitative parametric measures. The statistical differences between the means for related samples was performed using Friedman test. Ranked Spearman correlation test to study the possible association between each two variables among each group for non-parametric data.

The probability of error at 0.05 was considered sig., while at 0.01 and 0.001 are highly significant.

RESULTS

This study included 22 patients with spasticity due to cerebral palsy, 14 were diplegic and 8 were hemiplegic (4 were Rt sided, 4 were Lt sided) , 12 males and 10 females, 3 patients had upper limb affection in addition to lower limb. Descriptive data of the patients were presented in table 1.

Comparison baseline data with one and six months using Friedman test after Botox A injection revealed significant change in all variables except for MAS TP from baseline as primary outcomes (Table 2).

Table 2 showed a significant increase in ROM knee and ankle after 1 month and after 6 months post Botox injection, with main improvement at 1 month with smaller improvements thereafter, as it was shown by the mean rank values (Figure 1). In addition, there was a significant reduction in Pain score and modified Ashworth score of Gas, Ham and TP muscles across the time with no change between one month and six month. Moreover, TMW increase significantly one month while no change after 6 months. Also, amplitude of H/M and F/M significantly decreased across time of the study which was more evident in F/M at the 6 months intervals. IP activity of gastrocnemius revealed significant increase across the 2 time intervals.

Twelve patients were able to ambulate without any

Table 2. Comparison mean ranks baseline versus one and six months post injection.

Patients Data	Base Mean Rank	Base Range	1m Mean Rank	1 m Range	6 ms Mean Rank	6ms Range	X²	P	S
ROM Ankle	1.21	-20 , 25	2.29	-10 , 25	2.50	-5 , 25	28.20	0.00	S
ROM knee	1.11	-40:0	2.39	-20:0	2.50	-20:0	30.56	0.00	S
MAS Gas	2.80	1 , 4	1.60	1 , 3	1.60	1 , 3	32.00	0.00	S
MAS Sol	2.80	1 , 4	1.60	1 , 3	1.60	1 , 3	32.00	0.00	S
MAS Ham	2.80	1 , 4	1.60	1 , 3	1.60	1 , 3	32.00	0.00	S
MAS TP	2.10	1 , 3	1.95	1 , 2	1.95	1 , 2	4.00	0.14	NS
Pain score	2.50	0 , 3	1.75	0 , 2	1.75	0 , 2	12.00	0.00	S
TMW	2.91	20 , 70	1.59	12 , 60	1.50	10 , 60	18.24	0.00	S
H/M	2.71	3 , 66	1.53	1 , 50	1.76	1.8 , 50	17.45	0.00	S
F/M	2.58	13 , 100	1.82	5 , 100	1.61	6 , 100	12.03	0.00	S
IP(Gas)	1.68	20 , 348	1.74	14 , 350	2.58	14 , 340	11.20	0.00	S



Figure 1. Clinical improvement of knee and ankle ROM during standing and walking.
A: Diplegic CP child with tip toeing gait before injection and flexed knees.
B: Same child after Botox injection with heels on the ground and better knee extension.

support in all the follow up assessments. Four patient who needed support when walking at baseline and one month post injection, can walk independently at the end of the study. The remaining six patients were unable to walk without assistance at any time interval of the study.

A Spearman's correlation was done to study the relation between critical variables of lower limbs spasticity at 6 months (MAS Gas, MAS Sol, MAS Ham) with patients demographic, clinical and neurophysiological

data at baseline (Table 3).

This table showed a significant negative correlation between MAS of (Gas, Sol and Ham) at 6 months and baseline ROM knee and ankle as well as between MAS Gas, Sol and baseline interference pattern of gastrocnemius.

Moreover, to find out dependable factors of primary outcomes, the percentage of change of both MAS Gas and Sol (as treatment outcome) across the study duration were studied and showed significant negative correlation

Table 3. Correlation between modified Ashworth score at 6 months and baseline patients variables.

Patients data	MAS2 Gas		MAS2 Sol		MAS2 Ham	
	r	P	r	P	R	P
Age	-0.284	0.426	-0.190	0.599	-0.228	0.527
Weight	-0.118	0.746	-0.037	0.919	-0.363	0.302
Duration after injury	-0.406	0.245	-0.309	0.384	-0.116	0.749
ROM Ankle	-0.747	0.000**	-0.566	0.009**	-0.350	0.130
ROM Knee	0.562	0.010*	-0.677	0.001**	-0.896	0.000**
Pain Score	0.200	0.579	0.111	0.761	0.047	0.898
TMW	0.026	0.944	0.032	0.930	0.256	0.475
H/M	0.213	0.367	0.038	0.873	0.175	0.460
F/M	0.095	0.689	0.056	0.815	0.273	0.245
IP Gas	-0.448	0.048*	-0.499	0.025*	-0.278	0.235

* is significant

** is high significant

Table 4. Correlation between TMW2 and patients variables at baseline and 6 months post injection.

Baseline	TMW 2		6 months	TMW2	
	r	p		r	p
Age	0.032	0.920	Age	0.032	0.920
Weight	-0.037	0.909	Weight	-0.037	0.909
Duration	0.065	0.841	Duration	0.065	0.841
ROM Ankle	-0.040	0.912	ROM Ankle	-0.112	0.759
ROM Knee	-0.652	0.041*	ROM Knee	-0.800	0.005**
MAS Gas	0.233	0.518	MAS Gas	0.282	0.429
MAS Sol	0.272	0.447	MAS Sol	0.323	0.362
MAS Ham	0.525	0.119	MAS Ham	0.599	0.049*
MAS TP	0.180	0.619	MAS TP	0.243	0.498
Pain Score	0.367	0.241	Pain score	0.261	0.413
H/M amp	0.877	0.000**	H/M	0.011	0.976
F/M amp	0.197	0.585	F/M	0.701	0.024*
IP	-0.211	0.558	IP	-0.217	0.547

* significant ** high significant TMW 2: TMW after 6 months

with patient's age ($r = -0.837$, $p = 0.003$, $r = 0.818$, $p = 0.004$) respectively, and duration after injury ($r = -0.858$, $P = 0.002$, $r = -0.838$, $P = 0.002$) respectively.

Secondary outcomes were functional improvement represented by TMW (sec) and Interference pattern. There was a significant decrease in TMW and increase in IP GAS at the end point of the study ($\chi^2 = 18.24$, $p < 0.01$, $\chi^2 = 11.20$, $p = .00$) respectively.

Further analysis of factors affecting TMW2 as a secondary outcome at the end point of the study was addressed, so correlation between TMW2 and all patients' clinical and neurophysiological variables

concerning spasticity was done (Table 4).

This table showed that TMW2 was significant negatively correlated with initial ROM knee and highly significant correlated with knee ROM at 6 months. Moreover, TMW2 was highly significant positively correlated with initial H/M amplitude while significant correlated with F/M amplitude and with MAS Ham at 6 months.

It was concluded that initial ROM knee, initial amplitude of H/M and post injection ROM knee, F/M amplitude and MAS Ham were dependable factors for TMW2 at the end of study as a secondary outcome.

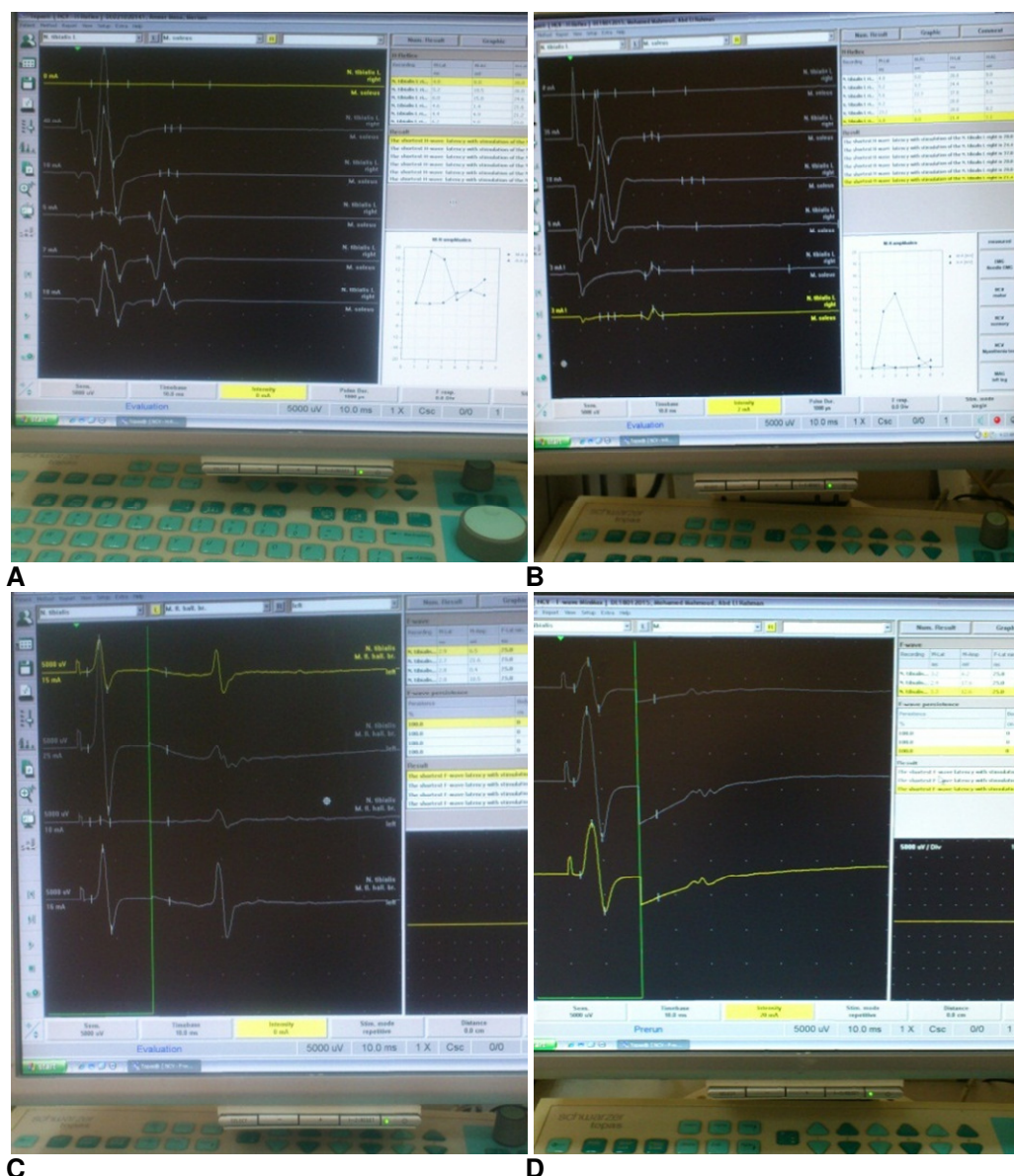


Figure 2. Electrophysiological changes in H/M, and F/M ratios.

A: Increased H Reflex amplitude before botox injection. **B:** Decreased H Reflex amplitude after botox injection. **C:** Increased F wave amplitude before botox injection. **D:** Decreased F wave amplitude after botox injection.

DISCUSSION

Treatment with Botox- A was very effective in correcting the position of the spastic lower limb (knee and ankle), as shown by proper standing (heels on ground and extended knee), confirming the findings of previous studies (Russma et al., 2002, Fazzi et al., 2005). Our results revealed significant reduction in pain score, TMW, modified Asworth score of gastrocnemius, soleus muscles, as well as H/M amplitude and F/M amplitude in both sides. While a significant increase in ROM ankle and

knee and interference pattern activity (resisted active maximal volition) in both sides. Decreased H/M and F/M ratios revealed decrease spasticity while increase in IP (resisted active maximal contraction) revealed better voluntary contraction of the patient muscle.

An obvious improvement in spasticity clinical measures, gait speed, and electrophysiological measures was noticed and these improvements persisted up to 6 months. This is not only due to weakening of the spastic muscles but also due to the increase in length of muscle tendon unit with subsequent shortening of the antagonist

muscles (Camargo et al., 2009).

We found significant increase in ROM knee and ankle as well as significant reduction in TMW mainly after 1 month post Botox injection, with smaller improvements thereafter as it was shown by the mean rank values. In addition, there was a significant reduction in Pain score, and modified Ashworth score of Gas, Sol and Ham and TP muscles in the first month which persisted with no change between one month and six months. This may be explained by the lack of 2nd session injection therapy and dilution effect of newly restorated Acetyl choline neurotransmitter after 3 months of BOTX A injection.

Although the duration and effect of Botox –A reported in the literature varies, it is generally considered to be effective for at least three months (Hawamdeh et al., 2007). That is in agree with study of Unlu et al. (2010) found that the muscle tone of the hip flexors, adductors, knee flexors and ankle plantar flexors was significantly reduced at the three-month assessment. However, this effect on spasticity did not last until the end of the sixth months because muscle tone increased between the three- and six-month evaluations (Koman et al., 2001). Moreover, Scholtes et al., (2007) observed a reduction in spasticity beginning six weeks after multilevel injections and showed that the lack of this effect at 24 weeks post-injection supported the temporary effect of the toxin due to the restoration of neuromuscular junctions).

Also amplitude of H/M was minimally raised at 6 months after being significantly decreased. This could be attributed to the smaller dose injected in soleus muscle (2-3U/kg), which is the recording site of H reflex, as the total injected dose (200-300 U/session) was divided among five muscles (Gas, Sol, medial and lateral Ham and TP). Moreover, the smaller dose injected in the soleus muscle relative to low baseline MAS Sol (2.45 ± 0.8). On the other hand, IP activity of gastrocnemius revealed progressive significant increase across the 2 time intervals. This may be due to that the IP is under voluntary control and this was previously explained by Pandyan et al. (2002), who reported that improvement in voluntary control was contrary to the expected weakening following treatment with botulinum toxin type A and suggests an optimization of motor control.

Manganotti et al. (2007), evaluated the effect of BTX-A injection on spastic equinus foot in CP patients and showed a significant decrease in Ashworth scale score's and an increase in the range of motion of the ankle joint at the end of the first month, which was supported by both pedobarometry and surface EMG findings.

Our results were in agree with Albani et al. (2010), who studied Ten patients and were assessed before, 30 days and 180 days after BTX injection. At 30 days all clinical measures improved significantly. Whereas MAS scores, were worse at the second assessment, global pain scale

improved over time, both at the first and at the second evaluation session. A reduction of surface EMG activity (parameters indicative of spasticity) was found 30 days after injections. The results of the EMG demonstrated the maintenance over time of the spasticity reduction recorded at T30. Thus, at T180, while the semi-quantitative evaluation of tone would seem to indicate the reappearance of spasticity, the quantitative EMG evaluation clearly indicated maintenance of the positive effects, suggesting that the next BTX administration could be postponed.

Furthermore, we found a strong relation between patients' age as well as disease duration and the reduction of MAS (Sol, Gas) at the end of study as primary outcome. This is in common with previous studies as with younger children, it might be easier to maintain the functional gains because the motor pattern of younger children provides better development due to increased plasticity of the central nervous system (Russma et al., 2002). Moreover, baseline ROM knee, baseline amplitude of H/M and post injection both F/M amplitude as well as MAS Ham were dependable factors for TMW2 at the end of study as a secondary outcome. This was obvious by its correlation with spasticity's clinical and electrophysiological measurement variables.

CONCLUSION

Our study ascertain the efficacy of a multilevel Botox injection approach for spastic CP children in a single session therapy which help the restoration of the normal neuromuscular system controlling tone, power and function of the spastic muscles as we did reliably measure them. Nevertheless, sustained physiotherapy regimen (stretching, strengthening and gait training) did achieve the favorable outcomes.

We recommend to combine neurophysiological measures with clinical descriptive scales assessment in pediatric spastic CP children as measurement of EMG activity may be an effective means of detecting functional improvements and of monitoring the effects of treatment.

STUDY LIMITATIONS

The small number of patients which was due to financial issues (cost of BOTOX-A) and lack of control group (placebo injection), are among the limitations of the present work.

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