Long-Term Improvement on GMFCS Level of Patients with Cerebral Palsy Treated by an Integrated Approach of Repeated Botulinum Toxin-A Injections

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INTRODUCTION

- Children with cerebral palsy (CP) can exhibit a wide variety of clinical presentations, and there are several proposed ways of classifying the disorder.
- One of the most commonly used methods of classification is the Gross Motor Function Classification System (GMFCS) which categorizes CP severity on the basis of self-initiated movement abilities, with particular focus on sitting, walking, and wheeled mobility. The scale consists of five levels of function, from most able as level I to least able as level V.[1]
- It is generally agreed that children with CP reach their gross motor potential by the age of 3.5-5 years. After this time, the GMFCS is classically considered to be longitudinally stable.[2] For example, a child aged >5 years old who is classified at a Level IV is likely to require a mobility device throughout his or her life.
- Treatment with botulinum toxin-A (BoNT-A) is an important and valuable treatment in children with CP because it is safe in young children and allows combined treatment with other treatments including orthoses, casting, conventional therapies and activity based functional trainings.[3-6]

OBJECTIVE

- In our specialist clinic, we observed GMFCS changes in our patient population with management of hypertonia by BoNT-A in an integrated model.
- The aim of this retrospective study was to evaluate the changes in GMFCS levels of children with CP who received repeated BoNT-A injections within an integrated treatment approach.

METHODS

Setting

- This was a retrospective, single-centre, observational study conducted at the Kocaeli University Department of Physical Medicine and Rehabilitation (PMR) and Izmit Rehabilitation Center.
- In this setting, injection parameters are individualized according to the goals of treatment, motor severity, accompanying disturbances, age and weight of the patient, body region, the size of the targeted muscle(s), neuro-muscular junction distribution for the muscle(s) and previous BoNT- A experience.
- All children are managed by a multidisciplinary team consisting of PMR physicians, physical therapists, occupational therapists and students, special education specialists, recreational sports specialists, and orthotists.

Inclusion criteria and treatment

- All children with a diagnosis of CP and lower limb hypertonia treated with at least 2 BoNT-A treatment cycles within an integrated rehabilitation program between 2007 to 2017 were included in this study.
- Following each BoNT-A injection, entered a 3-week intensive rehabilitation program (half day or full day), which could have been extended for a further 3 weeks if robotic rehabilitation was employed.
- The program usually started 7 to 10 days after BoNT-A injection, and was designed by the senior PMR physician according to individualized therapeutic goals.

RESULTS

Patient disposition and treatment

- Retrospective analysis of case records identified 503 children with CP who fulfilled the inclusion criteria for this study.
- During this time period patients received 2- 18 BoNT-A treatment cycles with BoNT-A (mean ± SD of 4.19 ± 2.9 cycles).
- Overall, 91.8% had orthotics, 58.6% received biodex balance training, 58.6% whole body vibration, 45.3% intermittent or weekly progressive serial casting, 44.9% virtual reality training, 40.2% hippotherapy, 12.7% robotic rehabilitation, 10% dance therapy and 8.5% functional intensive ambulatory training,
- Overall, 47.5% of patients received onabotulinumtoxinA (onaBoNT-A), 32.0% received both onaBoNT-A and abobotulinumtoxinA and 20.5% received aboBoNT-A in their repeated injection treatment cycle.

Baseline characteristics and associated conditions

Baseline Characteristics	
Gender, n (%)	
Girls	201 (40)
Boys	302 (60)
Age (years), (Mean ± SD)	5.52 ± 3.5
Type of hypertonia, n (%)	
Spastic	371 (73.8)
Mixed	132 (26.2)
Type of involvement, n (%)	
Unilateral	101 (20.1)
Bilateral	402 (79.9)
Associated Conditions n (%)	
Intellectual disability	73 (14.5)
Epilepsy	101 (20.1)
Speech and communication difficulties	107 (21.3)
Swallowing problems	111 (22.1)
Behavioral disorders	51 (10.1)
Bladder and/or bowel incontinence	175 (34.8)
Strabismus and/or visual disorders	228 (45.3)

Mean ± SD dosages per muscle (U/kg) in 2124 injection episodes

Dose per muscle (n=OnaBoNT-A/AboBoNT-A)	OnaBoNT-A treatment cycles (n=1409)	AboBoNT-A treatment cycles (n=715)
Iliopsoas (n=894/854)	0.8 ± 0.4	2.2 ± 0.9
Hip adductors (n=1408/545)	1.2 ± 0.6	2.5 ± 1.1
Rectus femoris (n=1308/754)	1.3 ± 0.7	2.3 ± 1.1
Gracilis (n=1618/905)	1.1 ± 0.7	2.5 ± 1.0
Hamstrings (n=2035/1091)	2.0 ± 1.0	4.7 ± 2.1
Gastrocnemius (n=2220/1193)	2.6 ± 1.2	5.7 ± 2.5
Soleus (n=1342/867)	1.4 ± 0.7	3.2 ± 1.5
Tibialis posterior (n=1015/678)	1.2 ± 0.6	2.8 ± 1.3
Peroneal muscles (n=514/345)	0.9 ± 0.5	2.0 ± 0.8
Flexor digitorum longus (n=322/525)	0.6 ± 0.3	1.6 ± 0.6
Tibialis anterior (n=19/55)	0.5 ± 0.1	1.7 ± 0.7
Flexor hallucis longus (n=61/81)	0.4 ± 0.2	1.2 ± 0.4
Flexor digitorum brevis (n=40/56)	0.4 ± 0.2	1.4 ± 0.8
Other muscles (n=22/16)	0.5 ± 0.3	1.2 ± 0.5

OnaBoNT-A:Onabotulinumtoxin-A; AboBoNT-A:Abobotulinumtoxin-A

Efficacy findings

- After repeated and integrated BoNT-A treatment, 42.3% of children had at least one level of GMFCS improvement, with worsening seen in only 3 patients.
- Of note, 8.5% of the GMFCS III/IV patients had two levels of GMFCS improvement.
- The improvement in GMFCS scores was statistically significant ($p<0.001$).
- Type of involvement ($p<0.001$), type of hypertonia ($p=0.031$), baseline GMFCS level ($p<0.001$) were found to be the predictors for improvement in GMFCS level, but not age and gender.

Improvements in Gross Motor Function Classification System (GMFCS) Scores

End of study GMFCS / Baseline	I n(%)	II n(%)	III n(%)	IV n(%)	V n(%)	Total N
I	17 (100%)					**17**
II	60 (42%)	82 (57.3%)		1 (0.7%)		**143**
III	5 (6.3%)	39 (48.8%)	36 (45.0%)			**80**
IV		22 (9.2%)	74 (31.1%)	140 (58.8%)	2 (0.1%)	**238**
V				12 (48.0%)	13 (52.0%)	**25**
Total N	**82**	**143**	**110**	**153**	**15**	

Modified Ashworth and Tardieu Scale scores (4-6 weeks post injection) at Treatment Cycles 1 and 2

	Baseline (TC 1)	Change from baseline (TC 1)*	Baseline (TC 2)	Change from baseline (TC 2)*
Hip adductors (Flexed knee)				
MAS (n=255)	2.9 ± 1.0	1.7 ± 0.6	2.8 ± 0.9	1.7 ± 0.7
TS (n=195)				
XV1	43.4 ± 12.2	9.9 ± 7.8	45.4 ± 12.0	9.5 ± 7.7
XV3	24.8 ± 10.9	18.4 ± 10.6	26.0 ± 11.2	19.3 ± 10.5
X	18.6 ± 7.0	8.3 ± 8.9	19.4 ± 7.2	9.8 ± 8.5
Y	2.0 ± 0.0	0.5 ± 0.9	2.0 ± 0.0	0.6 ± 0.9
Hip adductors (Extended knee)				
MAS (n=322)	3.0 ± 0.9	1.6 ± 0.6	2.9 ± 0.9	1.6 ± 0.6
TS (n=265)				
XV1	33.8 ± 12.2	9.5 ± 6.8	35.6 ± 11.2	8.6 ± 7.0
XV3	17.6 ± 10.6	15.7 ± 8.5	19.4 ± 10.4	15.8 ± 8.5
X	16.2 ± 6.4	6.13 ± 7.7	16.2 ± 6.6	7.2 ± 7.6
Y	2.0 ± 0.0	0.4 ± 0.8	2.0 ± 0.0	0.5 ± 0.9
Hamstrings				
MAS (n=405)	3.2 ± 0.8	1.6 ± 0.6	3.1 ± 0.8	1.6 ± 0.6
TS (n=350)				
XV1	124.9 ± 21.2	20.4 ± 12.1	129.5 ± 21.1	18.4 ± 10.7
XV3	96.1 ± 23.0	31.4 ± 14.8	103.5 ± 24.8	28.8 ± 14.3
X	28.8 ± 12.2	11.8 ± 14.3	26.2 ± 11.8	10.5 ± 11.9
Y	2.0 ± 0.0	0.3 ± 0.7	2.0 ± 0.1	0.3 ± 0.7
Plantar flexors (Flexed knee)				
MAS (n=463)	3.4 ± 0.6	1.8 ± 0.6	3.2 ± 0.7	1.8 ± 0.6
TS (n=395)				
XV1	92.6 ± 11.8	11.6 ± 7.6	95.7 ± 10.9	10.1 ± 7.0
XV3	66.1 ± 14.8	22.6 ± 11.0	70.9 ± 13.9	21.3 ± 10.2
X	26.7 ± 10.8	11.1 ± 9.6	25.0 ± 10.2	9.9 ± 25.8
Y	2.1 ± 0.4	0.2 ± 0.6	2.1 ± 0.3	0.2 ± 0.6
Plantar flexors (Extended knee)				
MAS (n=460)	3.6 ± 0.6	1.7 ± 0.6	3.4 ± 0.6	1.7 ± 0.6
TS (n=392)				
XV1	82.1 ± 12.6	11.9 ± 7.8	85.4 ± 11.5	10.7 ± 6.8
XV3	55.0 ± 14.6	23.4 ± 10.9	60.2 ± 14.6	21.5 ± 10.1
X	27.1 ± 9.9	11.6 ± 9.8	25.4 ± 9.7	11.0 ± 9.6
Y	2.1 ± 0.3	0.1 ± 0.4	2.1 ± 0.3	0.2 ± 0.5

* $p<0.001$ for all parameters. All data are mean ± SD. MAS: Modified Ashworth Scale. MAS scores were derived as 0=0, 1=1, +1=2, 2=3, 3=4 and 4=5. TS: Tardieu Scale. XV1: Angle of arrest at slow speed, XV3: Angle of catch at fast speed, Y: Spasticity grade, X: Spasticity angle

CONCLUSION

- The results of this study showed that at least 40% of children with CP have the potential for improvement in their GMFCS level when repeated BoNT-A injections were combined with intensive rehabilitation programs.

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