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Original Article

Others Section

Effect of Botulinum Toxin Type A on Functional Mobility in Cerebral Palsy with Lower Limb Spasticity

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ABSTRACT

Introduction: Children with Cerebral Palsy (CP) often start walking much later than typically developing children and they do so with a slower speed and higher energy cost. Mobility varies across different environmental settings and Functional Mobility Scale (FMS) was devised to illustrate functional mobility in these children over three distinct distances, chosen to represent mobility in the home, at school and in the wider community. Botulinum toxin A injections into the gastrocnemius muscle for equinus foot deformity, as well as multilevel lower limb injections have shown improvements in gait, however, there is paucity of literature on its effect on functional mobility.

Aim: To study the efficacy of Botulinum toxin A injection in CP with lower limb spasticity in terms of reduction in spasticity and effect on functional mobility.

Materials and Methods: A total of 31 children were enrolled and evaluated for various outcome measures just before injection and at 4 and 12 weeks after injection. Change in FMS on follow-up was analysed using Wilcoxon signed-rank test. Spearman's correlation analysis was performed between the number of injected muscles in each child and change in FMS scores on follow-up. A p-value of <0.05 was considered statistically significant. Analyses were done using SPSS version 21.0 statistical software (IBM Corp., Armonk, NY).

Results: At distances of 5, 50 and 500 meters, FMS showed statistically significant improvement at four weeks (p-value <0.001 at 5; 0.002 at 50; 0.006 at 500 meters) and at 12 weeks (p-value <0.001 at 5; 0.001 at 50; 0.002 at 500 meters) compared with baseline but no significant change from 4 to 12 weeks (p-value=0.102 at 5; 1.000 at 50; 0.157 at 500 meters). There was moderate positive correlation between the number of injected muscles in each child and the change in FMS from baseline to 12 weeks at 5 meters distance; however, a moderate negative correlation was observed for the same at 500 meters.

Conclusion: Local injection of Botulinum toxin A is effective in reducing the lower limb (gastrocnemius, hamstring, adductor) spasticity in CP children. It also improves the FMS in CP children.

Keywords: Cerebral palsy, Functional mobility scale, Spasticity

INTRODUCTION

Cerebral palsy includes a group of posture and movement disorders that occur as a result of a non-progressive disturbance in the developing fetal or infant brain [1]. Children with CP often start walking much later than typically developing children and they do so with a slower speed and higher energy cost [2,3]. Mobility of CP children varies across different environmental settings and FMS was devised to illustrate functional mobility in these children over three distinct distances, chosen to represent mobility in the home, at school and in the wider community [4]. This scale rates the child's functional mobility on a scale of 1 to 6 over three distinct distances-5 meters (for example: Household, Classroom), 50 meters (for example: an empty hallway) and 500 meters (for example: Mall, Grocery store). Spasticity is common in CP children and isolated Botulinum toxin A injections into the gastrocnemius muscle for equinus foot deformity, as well as multilevel lower limb injection have shown improvements in gait and gross motor function [5]. Use of Botulinum toxin A injection to hamstrings in CP children with crouch gait results in muscle lengthening [6]. A randomised double-blind, placebo-controlled trial in CP children with lower limb spasticity demonstrated that injection with Botulinum toxin A results in improved gait function and partial denervation of the injected muscle [7]. FMS is a reliable tool that can be used by clinicians to assess mobility in children with CP [8]. There is a paucity of literature in India for the use of Botulinum toxin A injection for improvement in functional mobility in CP children. Hence, our study was conducted with the aim to study the efficacy of Botulinum toxin A injection in children with CP with lower limb spasticity and its effect on functional mobility in a tertiary care government hospital in North India.

MATERIALS AND METHODS

An Interventional cohort study was conducted in the Outpatient Department (OPD) of the Department of Physical Medicine and Rehabilitation of Safdarjung Hospital, New Delhi, from 26 December 2013 to 25 December 2014 year after taking due approval from the Institute Ethics Committee. All CP children aged ≥2 years with lower limb spasticity of Modified Ashworth Scale (MAS) ≥2 for gastrocnemius and hamstrings and/or Adductor Tone Rating Scale ≥2 for hip adductor spasticity, and who can walk independently or with support (stick/crutch/rollator) were enrolled in the study after taking informed consent from parents. However, those CP children with contracture or prior surgery of lower limb, spasticity in the soleus muscle, taking antispastic medications, Botulinum toxin injection in the past six months and unable to follow commands were excluded from the study. Oral sedation with triclofos sodium syrup (500 mg/5 mL) in the dose of 250-500 mg (for 2-5 years of age) and 500-1000 mg (for 6-14 years) and not exceeding 70-120 mg/kg was given to these children 30 minutes prior to injection, to ease anxiety after which needle placement was done by anatomical knowledge and palpation of targeted muscle. Reconstitution of each vacuum-dried vial (100 units) of Botulinum toxin A, available free of cost in our hospital supply, was done with 2 mL of sterile 0.9% sodium chloride injection which was administered within 24 hours of reconstitution. We used the lowest dose of Botulinum toxin A per unit body weight of the range suggested by Worldwide Education and Awareness for Movement Disorders [9]. Exercise program and splinting were continued. The outcome measures used were:

- Modified Ashworth scale for spasticity of gastrocnemius and hamstrings [10].
- Adductor Tone Rating Scale (ATRS) for hip adductor spasticity [11].
- Functional mobility scale [4].

All the enrolled children were evaluated for the different outcome measures just before injection, at 4 and 12 weeks after injection (0, 4 and 12 weeks).

Referring to the article by Raj K et al., the minimum required sample size with 10% margin of error and 5% level of significance is 26 patients [12]. To reduce the margin of error, total sample size was taken as 31.

STATISTICAL ANALYSIS

Categorical variables were presented in numbers and percentages and quantitative variables as mean±standard deviation (median, range). Normality of data were tested by Kolmogorov-Smirnov test. Non parametric tests were used if the normality was rejected. Change in spasticity (MAS, ATRS) on follow-up was analysed with chi-square test. Change in FMS on follow-up was analysed using Wilcoxon signed-rank test. Spearman's correlation analysis was performed between the number of injected muscles in each child and change in FMS scores on follow-up. A p-value of <0.05 was considered statistically significant. Analyses were done using SPSS version 21.0 statistical software (IBM Corp., Armonk, NY).

RESULTS

A total of 31 CP children aged from 4-14 years were enrolled in the study. Out of them, a total of 28 (90.3%) children were in the age group of 4-9 years. Majority of them were males numbering 27 (87.1%). All the enrolled children completed the study. Topographically, 21 (67.7%) were diplegics, 3 (9.7%) quadriplegics, 6 (19.4%) right hemiplegics and 1 (3.2%) left hemiplegic.

A total of 42 (14 each of bilateral, unilateral) gastrocnemius muscles had a spasticity of grade ≥2 on MAS and they were injected with Botulinum toxin A. Gastrocnemius spasticity was significantly reduced in the follow-ups at 4 and 12 weeks compared with baseline (p-value <0.001) but not statistically significant at 12 weeks compared to 4 weeks (p-value=0.592), even though there was improvement in few children [Table/Fig-1-3].

Six hamstring muscles (2 bilateral, 2 unilateral) had spasticity grade ≥2 on MAS and these were injected with Botulinum toxin A. Hamstring spasticity significantly reduced in the follow-ups at 4 and 12 weeks compared with baseline (p-value <0.007) but not at 12 weeks compared to 4 weeks (p-value=1.000) [Table/Fig-4-6].

Botulinum toxin A was also injected in hip adductor muscles that had spasticity grade ≥2 on the ATRS. A total of 15 (7 bilateral, 1 unilateral) adductor muscles were injected. Statistically significant reduction was seen in ATRS in the follow-ups at 4 and 12 weeks compared with baseline (p-value <0.001) but not at 12 weeks compared to 4 weeks (p-value=1.000) [Table/Fig-7-9].

According to the FMS, at baseline, 16 (51.5%) of the children walked without aids (FMS 6 or 5) at home, 14 (45.2%) at school, and 13 (41.9%) in the community setting. Walking aids (FMS 4-2) were used by 15 (16.1%) at home, 17 (54.8%) at school and 18 (58.1%) in the community. The scenario changed at 4 weeks with 18 (58.1%) children walking without aids at home, 17 (54.8%) at school and 16 (51.6%) in the community. During this period, a total of 13 (41.9%), 14 (45.2%) and 15 (16.1%) children were using walking aids at home, school and in the community respectively. At 12 weeks, the number of children walking with and without aids at home and school, remained the same as that was at 4 weeks, though there was an increase in the number of children walking on uneven surfaces. There was however an increase to 17 (54.8%) of children walking without aids, and a reduced number of children 14 (45.2%) walking with aids in the community [Table/Fig-10].

At different distances of 5, 50 and 500 meters, FMS showed statistically significant improvement at 4 weeks (p-value <0.001 at 5; 0.002 at 50; 0.006 at 500 meters) and at 12 weeks (p-value <0.001 at 5; 0.001 at 50; 0.002 at 500 meters) compared with baseline but no significant change from 4 to 12 weeks (p-value=0.102 at 5; 1.000 at 50; 0.157 at 500 meters) [Table/Fig-11].

	MAS at 0 weeks	Total	Spasticity in gastrocnemius on MAS at 4 weeks				p-value
			0	1	1+	2	
Spasticity in gastrocnemius pre-intervention (0 weeks)	2	20 (100.00%)	2 (10.00%)	12 (60.00%)	6 (30.00%)	0 (0.00%)	<0.001
	3	22 (100-00%)	0 (0.00%)	2 (9.09%)	6 (27.27%)	14 (63.64%)	
Total		42 (100.00%)	2 (4.76%)	14 (33.33%)	12 (28.57%)	14 (33.33%)	

[Table/Fig-1]: Reduction in gastrocnemius spasticity at 4 weeks follow-up in patients with spasticity Grade 2 and Grade 3 on Modified Ashworth scale pre-intervention (n=42). Chi-square test (p<0.05 is considered statistically significant) applied

	MAS at 0 weeks	Total	Spasticity in gastrocnemius on MAS at 12 weeks				p-value
			0	1	1+	2	
Spasticity in gastrocnemius pre-intervention (0 weeks)	2	20 (100.00%)	2 (10.00%)	13 (65.00%)	5 (25.00%)	0 (0.00%)	<0.001
	3	22 (100.00%)	0 (0.00%)	7 (31.82%)	5 (22.73%)	10 (45.45%)	
Total		42 (100.00%)	2 (4.76%)	20 (47.62%)	10 (23.81%)	10 (23.81%)	

[Table/Fig-2]: Reduction in gastrocnemius spasticity at 12 weeks follow-up in patients with spasticity Grade 2 and Grade 3 on Modified Ashworth scale pre-intervention (n=42). Chi-square test (p<0.05 is considered statistically significant) applied

	MAS at 4 weeks	Total	Spasticity in gastrocnemius on MAS at 12 weeks				p-value
			0	1	1+	2	
Spasticity in gastrocnemius at 4 weeks	0	2 (100.00%)	2 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.592
	1	14 (100.00%)	0 (0.00%)	14 (100.00%)	0 (0.00%)	0 (0.00%)	
	1+	12 (100.00%)	0 (0.00%)	4 (33.33%)	8 (66.67%)	0 (0.00%)	
	2	14 (100.00%)	0 (0.00%)	2 (14.29%)	2 (14.29%)	10 (71.43%)	
Total		42 (100.00%)	2 (4.76%)	20 (47.62%)	10 (23.81%)	10 (23.81%)	

[Table/Fig-3]: Reduction in gastrocnemius spasticity at 12 weeks follow-up compared with spasticity at 4 weeks follow-up (n=42). Chi-Square test (p<0.05 is considered statistically significant) applied

	MAS at 0 weeks	Total	Spasticity in hamstrings on MAS at 4 weeks		p-value
			1	1+	
Spasticity in hamstrings pre-intervention (0 weeks)	2	5 (100.00%)	4 (80.00%)	1 (20.00%)	0.007
	3	1 (100.00%)	1 (100.00%)	0 (0.00%)	
Total		6 (100.00%	5 (83.33%)	1 (16.67%)	

[Table/Fig-4]: Reduction in hamstrings spasticity at 4 weeks follow-up compared with spasticity at pre-intervention (n=42).
Chi-square test (p<0.05 is considered statistically significant) applied

	MAS at 0 weeks	Total	Spasticity in hamstrings on MAS at 12 weeks		p-value
			1	1+	
Spasticity in hamstrings pre-intervention (0 weeks)	2	5 (100.00%)	4 (80.00%)	1 (20.00%)	0.007
	3	1 (100.00%)	1 (100.00%)	0 (0.00%)	
Total		6 (100.00%	5 (83.33%)	1 (16.67%)	

[Table/Fig-5]: Reduction in hamstring spasticity at 12 weeks follow-up in patients with spasticity Grade 2 and Grade 3 on Modified Ashworth scale pre-intervention (n=06).
Chi-square test (p<0.05 is considered statistically significant) applied

	MAS at 4 weeks	Total	Spasticity in hamstrings on MAS at 12 weeks		p-value
			1	1+	
Spasticity in hamstrings at 4 weeks	1	5 (100.00%)	5 (100.00%)	0 (0.00%)	1.000
	1+	1 (100.00%)	0 (0.00%)	1 (100.00%)	
Total		6 (100.00%)	5 (83.33%)	1 (16.67%)	

[Table/Fig-6]: Effect on hamstring spasticity at 12 weeks follow-up compared with spasticity at 4 weeks follow-up (n=06).
Chi-square test (p<0.05 is considered statistically significant) applied

	ATRS at 0 weeks	Total	Spasticity in adductors on ATRS at 4 weeks			p-value
			0	1	2	
Spasticity in adductors pre-intervention (0 weeks)	2	9 (100.00%)	2 (22.22%)	7 (77.78%)	0 (0.00%)	<0.001
	3	6 (100.00%)	0 (0.00%)	4 (66.67%)	2 (33.33%)	
Total		15 (100.00%)	2 (13.33%)	11 (73.33%)	2 (13.33%)	

[Table/Fig-7]: Reduction in adductor spasticity at 4 weeks follow-up in patients with spasticity Grade 2 and Grade 3 on Adductor Tone Rating scale pre-intervention (n=15).
Chi-square test (p<0.05 is considered statistically significant) applied

	ATRS at 0 weeks	Total	Spasticity in adductors on ATRS at 12 weeks			p-value
			0	1	2	
Spasticity in adductors pre-intervention (0 weeks)	2	9 (100.00%)	2 (22.22%)	7 (77.78%)	0 (0.00%)	<.0001
	3	6 (100.00%)	0 (0.00%)	4 (66.67%)	2 (33.33%)	
Total		15 (100.00%)	2 (13.33%)	11 (73.33%)	2 (13.33%)	

[Table/Fig-8]: Reduction in adductor spasticity at 12 weeks follow-up in patients with spasticity Grade 2 and Grade 3 on Adductor Tone Rating scale pre-intervention (n=15).
Chi-square test (p<0.05 is considered statistically significant) applied

There was moderate positive correlation between the number of injected muscles in each child and the change in FMS from baseline to 12 weeks at 5 meters distance; however, a moderate negative correlation was observed for the same at 500 meters as shown in [Table/Fig-12].

The lowest dose of Botulinum toxin A per unit body weight of the range suggested by Worldwide Education and Awareness for Movement Disorders was used in our study [9].

	ATRS at 4 weeks	Total	Spasticity in adductors on ATRS at 12 weeks			p-value
			0	1	2	
Spasticity in adductors at 4 weeks	0	2 (100.00%)	2 (100.00%)	0 (0.00%)	0 (0.00%)	1.000
	1	11 (100.00%)	0 (0.00%)	11 (100.00%)	0 (0.00%)	
	2	2 (100.00%)	0 (0.00%)	0 (0.00%)	2 (100.00%)	
Total		15 (100.00%)	2 (13.33%)	11 (73.33%)	2 (13.33%)	

[Table/Fig-9]: Effect on adductor spasticity at 12 weeks follow-up compared with spasticity at 4 weeks follow-up (n=15).
Chi-square test (p<0.05 is considered statistically significant) applied

FMS	5 meters			50 meters			500 meters		
	Baseline	4 weeks	12 weeks	Baseline	4 weeks	12 weeks	Baseline	4 weeks	12 weeks
6	1	11	12	0	5	7	0	3	4
5	15	7	6	14	12	10	13	13	13
4	3	11	13	3	5	4	4	5	4
3	0	0	0	0	0	0	0	0	0
2	12	2	0	14	9	10	14	10	10

[Table/Fig-10]: Distribution of functional mobility scale scores at different distances (5, 50, 500 meters) over time.

	Mean±SD	Median	Minimum-maximum	p-value of comparison with baseline	p-value of comparison between 4 weeks and 12 weeks
FMS at 0 weeks at 5 meter distance	3.77±1.48	5.00	2-6		
FMS at 4 weeks at 5 meter distance	4.81±1.14	5.00	2-6	<0.001	0.102
FMS at 12 weeks at 5 meter distance	4.97±0.91	5.00	4-6	<0.001	
FMS at 0 weeks at 50 meter distance	3.55±1.46	4.00	2-5		
FMS at 4 weeks at 50 meter distance	4.13±1.5	5.00	2-6	0.002	1
FMS at 12 weeks at 50 meter distance	4.13±1.61	5.00	2-6	0.001	
FMS at 0 weeks at 500 meter distance	3.52±1.43	4.00	2-5		
FMS at 4 weeks at 500 meter distance	3.97±1.47	5.00	2-6	0.006	0.157
FMS at 12 weeks at 500 meter distance	4.03±1.52	5.00	2-6	0.002	

[Table/Fig-11]: Functional mobility scale status in patients injected with Botulinum toxin type A at the 5 meters, 50 meters, 500 meters at 0, 4 and 12 weeks (n=31). Wilcoxon Ranked Sum Test (p<0.05 is considered statistically significant) applied

Parameter	Spearman's rho (ρ)	p-value
Baseline to 4 weeks		
N and change in FMS at 5 meters	0.238	0.197
N and change in FMS at 50 meters	-0.260	0.158
N and change in FMS at 500 meters	-0.276	0.133
Baseline to 12 weeks		
N and change in FMS at 5 meters	0.376	0.037*
N and change in FMS at 50 meters	-0.253	0.170
N and change in FMS at 500 meters	-0.386	0.032*
4 weeks to 12 weeks		
N and change in FMS at 5 meters	0.092	0.621
N and change in FMS at 50 meters	0.087	0.641
N and change in FMS at 500 meters	-0.284	0.122

[Table/Fig-12]: Spearman's correlation analysis between the number of injected muscles (N) and change in functional mobility scale.
*Correlation is significant at the 0.05 level (2-tailed)

DISCUSSION

Spasticity, which is commonly seen in children with CP, can be managed by non-pharmacologic (physical therapy, casting and orthotic use), pharmacologic (oral, intrathecal and local injection) and surgical measures [13].

Botulinum toxin is a neurotoxin and the biological product of the action of the anaerobic bacterium, *Clostridium botulinum*. It has seven serotypes, A to G. It acts in the cytosol of nerve endings to cleave three polypeptides that cause exocytosis. The serotypes A and E cleave synaptosomal-associated protein (SNAP)-25 while serotypes B, D, F, and G cleave Vesicle-Associated Membrane Protein (VAMP), and serotype C cleaves both syntaxin and SNAP-25. The ability of Botulinum toxin to inhibit acetylcholine release at neuromuscular junctions accounts for its therapeutic action to relieve spasticity [14]. The neurotoxin is a 150-kDa single-chain protein that is secreted as a large complex with nontoxic Neurotoxin-Associated Proteins (NAPs). The 150-kDa Botulinum neurotoxin is configured and looped to form a di-chain comprising of a heavy chain and a light chain that are connected by a disulfide (S-S) bridge. Whereas the heavy chain is indictable for getting the whole molecule close to its target, it is the light chain that is accountable for its toxicity. The light chains bring about their toxicity by affecting the SNARE (Soluable N-ethyl-maleimide sensitive factor attachment receptor) proteins, synaptosomal associated protein with a molecular mass of 25-kDa (SNAP-25) and syntaxin which is a protein inserted into the plasma membrane protruding into the cytosol [15].

Use of Botulinum toxin A injection into the gastrocnemius has been shown to improve gait [7,16,17]. It has also been reported that there is improvement in hamstring length and knee kinematics in gait after Botulinum toxin A injection to hamstrings [6]. There has also been reduction in hip adductor spasticity where adductors were injected using Botulinum toxin A [18]. In our study also, there was a reduction in the spasticity of gastrocnemius, hamstrings and hip adductors after Botulinum toxin A injection.

Orthopaedic surgery based on preoperative gait analysis gave marked improvements in gait function as measured by FMS [19]. The combination of adductor release and chemodenervation for management of generalised lower limb spasticity, hip displacement and contractures of adductors in children with bilateral spastic cerebral palsy resulted in reduction of spastic hip subluxation and improvements in gross motor function, as determined by FMS [20]. In the current study also, the FMS of CP children improved after Botulinum toxin A injection.

None of the enrolled CP children used crutches while walking for the different distances at any point of time. This may be explained by the ease of use of sticks than crutches. Better support and hence, better safety might be responsible for preference of use of walkers over crutches [21]. The general practice of prescribing assistive devices other than crutches also might be an additional factor. The number of children walking on uneven surfaces (FMS 6) at different distances increased with time after Botulinum toxin A injection.

In this study, the FMS of CP children improved on follow-up. This is similar to the findings of Tieman B et al., where the preferred mobility method in CP children changed from those requiring more gross motor control to the ones requiring less gross motor control overtime. Changes both within the child and environment are hypothesised to impact changes in mobility methods [22]. Gross Motor Function Classification System (GMFCS) can predict walking performance as it has high correlation with FMS [23].

The more the number of muscles needing Botulinum toxin A injection in a single child, the more would be the energy cost for mobility for the same distance. When multiple muscles of lower limb were injected with Botulinum toxin A in a single child, we found the resultant reduction in spasticity was translated to functional mobility for short distances (5 meters) but not for longer distances (50 and 500 meters). This can be due to increased energy cost while walking outdoors on uneven surfaces compared with the even surfaces indoors [24]. Also, we found that the translation to improved functional mobility for short distances was observed at 12 weeks, but not at 4 weeks. This could imply that this translation is a gradual process.

This study is significant in the fact that the improvement in lower limb spasticity after Botulinum toxin A injection might have been influential in improving the FMS in this group of CP children. The training period for functional mobility in these children most likely will also be shortened. However, more frequent follow-ups such as at weekly intervals will be useful as it might help to ascertain the tapering of the effect of Botulinum toxin A on various parameters and exactly the point of the peak effect of the injection. Moreover, follow-ups for longer durations of time could be useful in determining the appropriate timing of re-injection. We therefore recommend further prospective studies with a larger sample size and longer duration.

LIMITATION

The sample size was small with follow-ups only at 4 and 12 weeks after Botulinum toxin A injection. Though many of the children used different walking methods at a particular environment, the FMS was used for functional mobility which takes into consideration only the most frequently used mobility method.

CONCLUSION

To the best of our knowledge, this is the first study in India looking into the functional mobility of CP children with lower limb spasticity after Botulinum toxin A injection. Local injection of Botulinum toxin A is effective in reducing the lower limb (gastrocnemius, hamstring, hip adductor) spasticity in CP children. It also improves the FMS in this group of children. Discussion regarding various mobility options with children and their families is recommended, with the understanding that the method of mobility that optimises participation in one setting may not be the preferred method in another. Efficiency, safety and environmental features such as distance and time, are important considerations when making decisions regarding goals and interventions for mobility.

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