

A Study of Effects of Intervention of Botulinum Toxin- A on Lower Limb in Children with Spastic Cerebral Palsy

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Abstract

Objective: Analysis of clinical gait pattern, change in spasticity and range of motion (ROM) in cerebral palsy patient (CP) with spastic lower limb muscle after injecting botulinum toxin- A.

Study Design: Prospective study

Methods: 28 children (18 male and 10 female) with spastic CP had problems in normal walking, aged 2–9 years (mean age 4.65 years), consecutively treated in the PMR department over a 2-year period, were prospectively followed-up and clinically assessed pre- and post-treatment (at 2 weeks and 2 months) both objectively and subjectively. Objective assessment included gait parameters -- stride length, cadence, velocity, step length, base of support; active and passive range of motion (ROM), (measured by goniometry) and spasticity on modified Ashworth scale. Subjective assessment was done by asking questionnaire in terms of comfort, ease of care, perineal hygiene, walking. Injections were given using clinical palpatory method on OPD basis. All patients received botulinum toxin-A injections, followed with exercises and activities and orthosis as needed.

Results: Significant improvement was achieved for spasticity reduction in gastrocnemius ($p < 0.001$), hamstring and adductor ($p=0.050$), ankle AROM & PROM ($p < 0.001$), active knee extension ($p=0.009$), popliteal angle ($p=0.015$) and percentage left and right foot contact ($p < 0.001$), whereas non-significant change was observed in step length, cadence, velocity, stride length, and base of support. Parents felt subjective improvement in most of the cases (>90%).

Conclusions: Botulinum toxin- A injection is effective in the treatment of spastic lower limb muscles for equinus/crouching/scissoring gait in cerebral palsy children. The treatment was feasible and easily implemented. Botulinum toxin- A injections were well tolerated, yielded no serious treatment-related adverse events.

Key words: Botulinum toxin-A, spastic cerebral palsy.

Introduction:

Cerebral palsy (CP), a group of permanent, non-progressive congenital neurological disorders, is characterised by the resulting effects on movement and posture. Graham argued that the basic definition of CP

should be extended to include the progressive nature of the musculoskeletal pathology. Motor impairments that result from the many neurological deficits in CP include neuromuscular and musculoskeletal problems of spasticity, dystonia, muscle contractures, bony deformities, incoordination, loss of selective motor control, and weakness. The stiffness of the lower limbs often deteriorates during development results in defective walking patterns like scissoring gait due to hip adductor tightness, crouched gait due to hamstring tightness and toe walking due to calf muscle tightness. Therefore, antispasticity treatment, plays an important role in treating the child with CP. There are numerous treatment options available for hypertonicity management which is characteristic feature of CP, including physical and occupational therapy, orthosis, oral medications like baclofen, tizanidine, dantrolene etc, chemodeneration tendon lengthening, and dorsal rhizotomy. Thus a stepped up management protocol is adopted, beginning with the more conserving options

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and reserving surgical option for older children and those cases where the stiffness and progressive deformities continues to hamper rehabilitation. Chemodenervation is commonly done by botulinum toxin-A (BTX-A), phenol and alcohol. BTX-A is potent neurotoxin produced by anaerobic bacterium *Clostridium botulinum* with serotype A. It causes chemodenervation and muscle relaxation by inhibiting acetylcholine release into the synaptic cleft thus blocking the neuromuscular junction. The denervation temporarily reduces muscle tone and provides an opportunity to effect changes in motor learning and cortical motor organisation. BTX-A, when compared with phenol for adductor spasticity, improves cadence, step length, and velocity during gait. Anatomic localisation of target muscles using palpation was the most common technique and injection can be done quickly; and pain was not commonly reported as an important factor after injection. To date, most randomised controlled trials on the effects of BTX-A injections have focused on treatment of the lower extremities, including the ankle flexors, knee flexors, and hip adductors in children with spastic diplegia and hemiplegia. The two most common impairments studied are spasticity and limitations in range of motion (ROM). The level of function has been assessed by observing gait or reviewing the results of motor and functional outcome scales. The most commonly used tool to assess spasticity is the modified Ashworth scale (MAS). Multiple randomised controlled trials have demonstrated reduced MAS scores after injection of BTX-A in ankle flexors, hamstrings, and hip adductors. Outcome measures were not similar, and different in different studies. This study was conceptualised to evaluate the effects of BTX-A injection on lower limb muscles especially in terms of clinical gait pattern, spasticity and ROM.

Materials and Methods

Type of study – Prospective study.

Study population - 34 spastic CP patients, 2 to 9 years aged of either sex, who attended the outpatient department (OPD) of Physical Medicine & Rehabilitation (PMR), at the All India Institute of Medical Sciences (AIIMS), New Delhi between 2009 and 2011. Patient selection was done with the following criteria:

Inclusion criteria:

1. Spastic cerebral palsy patients with involvement of lower extremity muscles e.g. adductor alone, calf alone, or adductor with medial hamstring or

adductor with calf muscle (gastrocnemius) or all three muscle group, having spasticity interfering in gait pattern e.g. scissoring gait due to adductors, crouched gait due to hamstring, toe walking due to calf muscles.

2. Age 2 to 9 years,
3. Willingness of the parents/ guardians to participate.

Exclusion criteria:

1. Fixed joint contractures or deformities.
2. Bleeding disorders.
3. Previous treatment with BTX-A within 6 months.
4. Concomitant treatment with phenol, alcohol or any neurolytic procedures.
5. Known allergy to BTX-A.
6. Spasticity not interfering with activity of daily living or walking.
7. Cognitive dysfunction to such an extent that the patient will not be able to cooperate or follow instructions.
8. Patient on aminoglycosides.

BTX-A, is approved by US FDA, for the treatment of spasticity in cerebral palsy patient. The ethical clearance was obtained from the institutional ethical committee prior to the commencement of this study. The patients were explained about the study and their written consent was taken. Then their clinical assessment (history and physical examination) was being done. There was at least one week pre study observation period (for conservative management). Before injecting BTX-A, assessment was done in following way:

Assessment of gait parameters:

- a) Stride length
- b) Cadence
- c) Velocity
- d) Step length
- e) Base of support
- f) Number of falls if any

Active ROM, passive ROM (measured by goniometry) and grading of muscle spasticity on MAS and adductor tone rating were noted.

Subjective assessment: Questionnaire in terms of comfort (feeling better than earlier), ease of care, perineal hygiene, walking. Answer was taken as yes/ no.

After that two post injection follow-up at 2 weeks and 2 months were done. At each follow-up outcome measures of both objective and subjective were noted.

No change in antispastic medication was done during the course of the study.

Modified Ashworth scale 15 (for spasticity grading of hamstring and gastrocnemius):

0: no increase in muscle tone

1: slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the ROM when the affected part(s) is moved in flexion or extension

1+: slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM

2: more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved

3: considerable increase in muscle tone, passive movement difficult

4: affected part(s) rigid in flexion or extension

Adductor tone rating (for adductor spasticity assessment):

0: No increase in tone.

1: Increased tone, hips easily abducted to 45° by one person.

2: Hips abducted to 45° by one person with mild effort.

3: Hips abducted to 45° by one person with moderate effort.

4: Two people required to abduct the hips to 45°.

Intervention:

BTX-A is marketed as Botox® (Allergan, Inc.), Dysport® (Ipsen Limited), a Chinese formulation, Hengli (Lanzhou Institute of Biologic Products), and Xeomin® (Merz Pharmaceuticals), Botox® was used (Allergan, Inc.) in this study in all patients because it was easily and widely available.

Botox® injection were administered under complete aseptic precaution. Injection site of muscle was chosen as per anatomical landmark near the site of motor innervations by clinical palpatory method. Following injections, the muscles was massaged and subjected to ROM exercise a few times. Patients were observed for 1 hour, post injection to evaluate possible adverse events (pain, bleeding, rash, allergic reaction and other

concerns) if any. Patients were instructed to contact us directly over mobile phone with concerns regarding possible side-effects if any. Patients and their caregivers were reviewed 2 weeks and 2 months following each injection protocol for assessment.

Dosage: 4 U/kg per muscle with maximum of 50 U per injection site. Dilution was done by dissolving 100 U in 2 ml (50 U/ml) 0.9% normal saline. Maximum dose given was 12U/ kg total body weight for different muscles injected in a sitting.

Injection procedure: It was done on OPD basis. Attention diversion (like songs on mobile, engaging the child in different talks e.g. stories, etc) of the child was done while giving injections to alleviate fear of injection and then injection was given under complete aseptic and sterile condition. Injections were given by 1ml tuberculin syringe (26 gauge needle). Localisation technique was solely on anatomical basis where muscle belly is most prominent i.e. at the site of motor point and localisation of the injecting needle through fascia of the target muscle. In some very anxious children, sedation with syrup promethazine hydrochloride or triclofos was given.

After BTX-A treatment, the children continued participating in routine physical therapy throughout the study period as doing earlier. Children were provided knee ankle foot orthosis (KAFO) with or without abductor bar, ankle foot orthosis (AFO).

PROM at ankle with the knee in maximum extension was evaluated, and the foot was held in supinated position to diminish subtalar motion and mid foot dorsiflexion. The heel was positioned in the palm with the forefoot on my forearm, ensuring that the calcaneus was in neutral and the foot was aligned with the tibia. Maximum passive dorsiflexion was measured by using manual goniometer.

AROM at ankle was obtained from the flexor withdrawal reflex to determine any change in ROM during treatment. It was ensured that foot did not deviate into inversion or eversion. Maximum active dorsiflexion was measured with manual goniometer.

Popliteal angle was measured between the femur and the tibia as measured after flexing the hip to 90 degrees.

Active knee extension was measured as angle between longitudinal axis of the femur and tibia .

Assessment of gait parameters:

Stride length, base of support and percentage length of foot contact were measured by direct floor technique, [For simplification and easy quantification of foot contact part of physician rating scale (PRS) in busy OPD setting, measurement of the percentage of foot contact length antero-posteriorly from heel to toe was done], by applying chalk powder on the feet of child. Measurement of base of support was obtained by calculation of perpendicular distance between the most medial point of the inner border of each foot. Stride length was measured as distance between 2 successive placements of the same foot.

For cadence, velocity, step length child was asked to walk over a measured 10 metre distance. Out of 3 best measurements median value was taken.

Number of steps and time taken to cover the 10 metre distance is noted and then cadence, velocity and step length were calculated arithmetically.

Statistical analysis:

This was a prospective study with two follow-up at 2-week and 2-month after ascertaining baseline values. Total sample size was twenty-eight (28). For descriptive studies, various statistical parameters like the mean, median, standard deviation and range were used for determining continuous variables and frequency, percentage and range were used for determining the categorical variables. Besides descriptive statistics, the comparison over period of time was done by applying repeated measures analysis followed by post hoc comparison by Bonferroni method. Besides this where data were not distributed normally, Friedman test was applied. The comparison between pre and post injection follow-up was done by applying Mc Nemar test for the follow-up at 2-week and 2-month.

Table 1: ROM at Knee

AROM	ROM 0 Week Median (minimum, maximum)	ROM 2Weeks Median (minimum, maximum)	ROM 2 month Median (minimum, maximum)	P
LAKE (n=6)	-17.5(-30,-5)	-7.5 (-20,0)	-5(-20,0)	.009
RAKE (n=6)	-17.5(-30,-5)	-7.5(-20,0)	-5(-20,0)	.009
LPA (n=6)	70(55,70)	60(55,60)	55(50,60)	0.015
RPA (n=6)	70(55,70)	60(55-60)	55(50,60)	0.015

(LAKE -Left active knee extension); (RAKE - Right active knee extension) (LPA-Left popliteal angle); (RPA- Right popliteal angle).

Log transformation was also applied where the data was not distributed normally and sample size was reasonable. P - value <0.05 was considered as significant.

Results

A total of 28 patients (18 diplegic, 10 hemiplegic), 18 male, 10 female, 2-9 years old (mean age 4.66 yrs) completed the study. Out of 18 diplegic, 8 patients were given injection in both gastrocnemius, 4 patients in bilateral (b/l) adductor and gastrocnemius, 3 in b/l adductor and hamstring, 2 patients in b/l hamstring and gastrocnemius, 1 patients in b/l hamstring and left gastrocnemius. All hemiplegics (7 left and 3 right hemiplegics) were given BTX-A injection in respective gastrocnemius only. Total 69 muscles (43, gastrocnemius, 14 adductors and 12 hamstrings) were injected(Fig 1 & Tables 1-4).

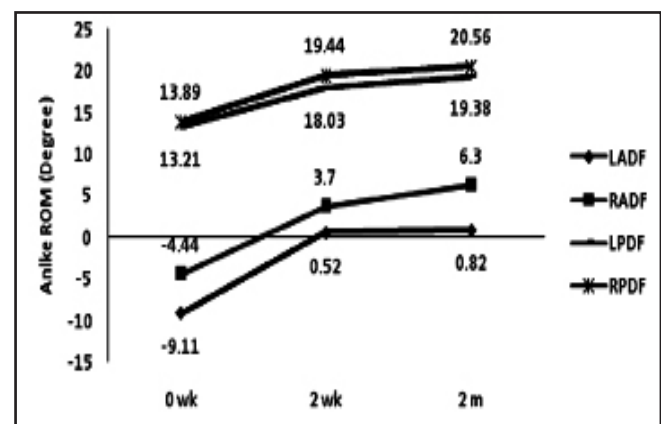


Fig1: ROM at Ankle (n= 28)

(LADF&RADF - left & right ankle active dorsiflexion; LPDF & RPDF- left & right ankle passive dorsiflexion) p<.001

Table 2: Gastrocnemius Spasticity

Muscle	Mean ± SD/0 week	Mean ± SD/ 2 week	Mean ± SD / 2months	P
LG (n=24)	2.92 ± 0.282	2.25 ± 0.442	2.08 ± 0.408	<.001
RG (n=19)	2.95 ± 0.229	2.26 ± 0.452	2 ± 0.471	<.001

(LF- left gastrocnemius, RG- left gastrocnemius)

Table 3: Hamstring and Adductor Spasticity

MUSCLE	Median (minimum, maximum)/0 week	Median (minimum, maximum)/2weeks	Median (minimum, maximum)/2months	P
LH (n=6)	2(1-3)	1(1-2)	1(1-2)	0.050
RH (n=6)	2(1-3)	1(1-2)	1(1-2)	0.050
LA (n=7)	2(1-3)	1(1-2)	1(1-2)	0.050
RA (n=7)	2(1-3)	1(1-2)	1(1-2)	0.050

(LH-left hamstring, RH- right hamstring, LA-left adductor, RA-right adductor)

Table 4: Gait Parameters

GAIT P	Mean±SD/0week	Mean±SD/ 2weeks	Mean±SD /2months	P
STR L (n=28)	48.16±12.67	48.45±11.33	50.64±10.63	.075
CAD (n=28)	95.16±43.88	94.47±41.46	101.22±36.50	0.210
VEL (n=28)	26.54±16.45	26.76±14.19	28.43±12.75	0.242
STEPL(n=28)	25.75±7.09	26.29±6.41	27.77±5.89	0.033
BS (n=28)	9.43±9.63	10.27±8.92	10.41±7.93	0.134
% LFC(n=28)	56.82±21.13	78.05±19.01	81.85±16.03	<.001
%RFC(n=28)	61.61±24.16	75.75±8.79	84.54±4.21	<.001

(STR L: Stride length, CAD: Cadence, VEL: Velocity, STEP L: step length, BS: Base of support LFC and RFC: left & right foot contact)

Subjective improvement: 27 out of 28 (96.4%) parents of patients felt comfort; 28 out of 28 (100%) parents felt improvement in ease of care ; 26 out of 28 (92.9%) parents of patients felt there is improvement in walking ; 7 out of 28 (25%) parents of patients were asked about improvement in perineal hygiene. All 7(100%) parents of patients reported subjective improvement in perineal hygiene at 2 week which remained till 2 months.

Side-effects: (1) Transient localised weakness-in one patient (BTX-A was injected in bilateral hamstring) (2) Flu like symptoms (fever) were noticed in two patients one day after injection which responded with in 2 days after taking syrup paracetamol.

Discussion:

Treatment with Botox® was effective in reduction of spasticity in the gastrocnemius, adductor and hamstring, increased active and passive ROM of the ankle joint, active knee extension confirming the findings of previous studies as described and discussed below.

Koman *et al*¹ showed that BTX-A treatment of the medial and lateral gastrocnemius muscles can reduce spasticity and improve gait and positioning in children with progressive dynamic equinovarus or equinovalgus foot/ankle deformities that were unresponsive to bracing. We also tried to correct these deformities with

bracing, physical and occupational therapy but got better result with intervention of BTX-A injection.

In a prospective, 3-month, randomised, double-blind clinical study by Koman *et al*² involving 114 children with CP and dynamic equinus foot deformity, patients in the Botox® group demonstrated improved ankle ROM, gait function and a 20% reduction in motor evoked potential (MEP) of the gastrocnemius muscle. The authors rated the predictability of improved gait function as low which is similar to our study.

Wissel *et al*³ found a significant improvement in Ashworth score ($p < 0.001$), knee ROM ($p < 0.01$) (passive 15°, active 20°) after BTX-A injections in multiple muscle groups, including the hamstrings, hip adductors, and ankle flexors. While gait analysis revealed significant increase in gait velocity ($p < 0.01$) and stride-length ($p < 0.001$) over baseline. In our study we did not get such improvement in velocity or stride. The reason could be less number of patients had injection in adductor and hamstring muscles

Fazzi *et al*⁴ observed a reduction in spasticity and an increase in passive joint mobility and scores on scales and tests intended to assess function. These improvements are reflected in the gait pattern (PRS), selective motor control in foot dorsiflexion, and the acquisition of new motor abilities.

Furthermore, the muscular relaxation achieved following application of BTX-A allows muscle-stretching exercises to be performed more easily and the child to learn to use and strengthen opposing muscles. For most children BTX-A helps delay shortening of the muscles. Specific therapeutic exercise treatment and orthosis can help the small percentage of children in whom there is evidence of prolonged muscle stretching. These are clear arguments for intensifying exercise therapy after the application of BTX-A to achieve better results in the long term as our patients did and could be able to tolerate easily.

Although the effects of BTX-A are seen primarily in a reduction of hypertonia, the changes in tone can improve the child's balance, strength, motor control and fixed contractures. As the child develops, the spastic muscles fail to grow as quickly as the neighbouring structures, and dynamic structures are transformed into fixed contractures. Relaxation of spastic muscles allows these to stretch, encourages their growth and prevents contractures. These improvements lead to functional gain.

It has been stressed that assessment of functional improvement is more important than assessment of the reduction in muscle tone or the increase in the ROM of the joint. The physiological and mechanical effects of BTX-A treatment are genuine and measurable in patients with spastic diplegia. However, these effects may not trigger a major change in function or change in the patient's or his/her parents' perception of function and thus not be recorded as a significant improvement in the patient's family and social life. But in our study there is great improvement in parents' perception of function; it may be due to early injection BTX-A (mean age 4.65 years) as well as less strictness of these improvement criteria.

We also observed an improvement on the foot contact component related to PRS scale after treatment; the beneficial effect was sustained until the end of the study. The scale sub items gait pattern and especially percentage of left and right foot contact, which are the two elements that are most closely related to spasticity of the gastrocnemius, improved significantly with BTX-A. Gait speed, the item with the greatest functional value on the scale, also improved but it was not significant statistically.

It was noticed that the non-significant improvement in gait speed, step as well as stride length is corroborating the findings in most of the studies done in CP patient. It may be due to more number of patients affected with gastrocnemius spasticity and less of adductor and hamstrings. Improvements in gait speed, step as well as stride length may also be contributed due to increased growth of the child especially in multiple and prolonged follow-up. On the contrary these improvements were noted significant in most of the studies done in post stroke spasticity as they tried better use to motor relearning because they knew their normal premorbid status.

Adductor injection may reduce scissoring, and knee flexor injection may aid knee straightening and improve standing ability. One class I study using BTX-A injection ($n=61$) into the adductors and medial hamstrings of CP patient showed an average improvement in knee-to-knee distance (fast catch) of about 9 cm ($p < 0.002$) and decrease in adductor spasticity on modified Ashworth scale of 2 ($p < 0.001$). Significant improvement noted both at 4 and 12 weeks. Two small open-label studies (class IV) found modest improvement in either gait kinematics or hamstring length with BTX-A injection into the hamstrings.

Corry *et al*⁵ injected BTX-A into 17 hamstrings in CP patients (mean age 7.2; Range 4 -11yr). In this study by Corry *et al*⁵ showed the median MAS score for hamstring were equally decreased. Spasticity at 0 week was 1(1-2) which decreased 1(0-2) at 2 weeks and 1(0-1) at 3 months. This change was not significant. In our study spasticity decreased by grade 1 in almost all patients but this was not significant statistically as only 6 children had hamstring spasticity.

Mean popliteal angle decreased by 16° at 2 weeks from mean±S.D of 64°(12.8) to 48°(11.3); and 17° at 3 months mean±S.D of 64°(12.8) to 47°(7.3); (n=10). It correlates with our finding as median decrease was 10° at 2 weeks and 15° at 2 months from 70° at baseline which is significant. The additional 5° decrease in mean popliteal angle can be attributed to muscular relaxation achieved following application of BTX-A allows muscle-stretching exercises more actively and easily. Our study noted improvement in the active knee extension of 10° at 2 weeks and 12.5° at 2 months from median baseline of -17.5°, almost similar to Corry *et al*⁵ study; this improvement was also noted qualitatively in stance phase. This means static improvement in active knee extension might be reflected dynamically in stance phase of the gait cycle.

So it is clear from various studies that BTX-A has a major effect on the dynamic spastic component but only limited effect on passive ROM, since the latter depends of resistance produced by muscle or joint connective tissue. In our study also more change is noted in AROM compared PROM, because some of our patients already had dorsiflexion passive ROM at ankle was ≥ 20°. We also believe that the increased effect of BTX-A at 2 months may also be related to the results of more aggressive therapeutic exercise.

In a recent study Carlos *et al*⁶ evaluated 20 children with spastic diplegic CP children. All the patients received injections in the gastrocnemius and soleus, and 15 received injections in the adductors. As like others they found decreased spasticity in gastrocnemius and adductors, decreased heel-ground distance, improved ambulation and equinus gait pattern, PRS (p<0.001). Gait speed also changed significantly as a result of the use of BTX-A (p<0.05).

Gait velocity in our study did not increase significantly, it may be explained by less number of adductor and hamstring injection in our study. The heel-ground distance is significantly decreased which may be correlated with increased percentage contact of foot to the floor of our study.

Degelaen *M et al*⁷ recently suggested, botulinum toxin injection in lower limb spastic muscles leads to changes in motor planning, including thorough interference with trunk stability, but a combination of therapies (orthosis and physical therapy) is needed in order to learn new motor strategies.

We assessed children from 2 to 9 years of age (mean 4.65 years), and our initial results were significant. With younger children we might have been able to maintain the functional gains because the motor pattern of very young children provides greater scope for better development and recovery (a younger child has greater potential than an older child for increasing the plasticity of the central nervous system).

A study by Wissel *J et al*³ revealed that of 33, 16 (48%) subjects reported improvement. Baker *et al*⁸ study showed more than half of parents reported good or minimal improvement. In our study parents reported subjective improvement in more than 90% of all cases that might be explained by younger children (mean age 4.44 years) and less strict subjective criteria followed in this assessment.

Most of the studies did not report any serious adverse; the rare side-effects were mild and transient with CP. In our study only one patient had fever. This is revealing that if BTX-A is injected properly, adverse effects are very minimal.

Conclusions:

BTX-A injection of the lower limb muscles was effective in the treatment of spastic equinus/crouching/scissoring in patients with CP. There was significant reduction in spasticity, popliteal angle and increase in ROM at ankle, active extension of knee. Percentage length of foot contact is increased. But evidence for improved walking is not so convincing in terms of gait velocity, stride length and cadence. Study limitations were short follow up, lack of control group and not verified the extent of physical exercise and orthosis wearing time.

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