Journal of Clinical Orthopaedics and Trauma 11 (2020) 208–212

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

Effect of botulinum toxin type-A in spasticity and functional outcome of upper limbs in cerebral palsy

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ARTICLE INFO

Article history:
Received 31 October 2019
Accepted 5 January 2020
Available online 8 January 2020

Keywords:
Cerebral palsy
Spasticity
Botulinum Toxin-A
MACS
COPM

ABSTRACT

Introduction: Spasticity has been considered to be a main contributor to both the impairment of function as well as posture in children with cerebral palsy (CP). Patterns of upper limb motor involvement in CP vary with resultant limitations in daily independence, participation, and quality of life. Botulinum Toxin-A (BTX-A) is a potent neurotoxin which acts by preventing the release of acetylcholine (Ach) from presynaptic axon at motor end plate reducing focal spasticity. With literature established role of BTX-A available for lower limb spasticity in CP, the purpose of this study was to present an objective analysis of the effect of a single i.m. injection of BTX-A in reduction of spasticity in the upper limb as well as functional outcome in children (4–12yrs) with spastic CP.

Methods: A total of 28 patients (30 upper limbs) of spastic CP with minimum follow up of 6months were included in the study. Modified Ashworth Scale (MAS) and Modified Tardieu Scale (MTS) were used to measure the spasticity. Surface landmarks were used to give I.m. Botox in selected spastic muscles followed by targeted rehabilitation. Functional outcomes were measured by MACS (Manual Ability Classification System) and Canadian Occupational Performance Measure (COPM) before treatment, at 3 and 6 months follow up.

Results: Pronator teres was the most frequently injected muscle followed by FCU and Adductor pollicis. MAS scores at all joints and MTS scores at forearm deteriorated between 3 and 6 months. However, MACS and COPM showed sustained improvement at 3months and 6months with statistically significant change.

Conclusion: I.m. BTX-A injected using anatomical landmarks had significant improvement in both clinical and functional outcome measures. We noticed significant improvement in MACS and COPM at 6 months despite return of local spasticity. It is safe and effective for spasticity of upper limbs in cerebral palsy and capable of improving function without major side effects. MACS & COPM are easy to use, less time consuming & easily adjusted to local needs. Randomized control trials with long follow up are required in future with special focus on dosing and timing, scoring system for functional outcome as per regional needs and issue for antibody formation for repeat injections of BTX-A.

1. Introduction

Cerebral palsy (CP) describes "a group of disorders of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain".[1] Although the brain lesion in cerebral palsy may be static, the secondary physical symptoms are progressive.[2,3]

Patterns of upper limb motor involvement in cerebral palsy vary according to the muscles affected, the degree of spasticity, the patient's age and any treatment taken or not. For children with hemiplegic CP, the effect on upper limb (UL) function is often more pronounced than that on lower limb function, with resultant limitations in daily independence, participation, and quality of life.[4-] Spasticity has been considered to be a main contributor to both the impairment of function and decreased longitudinal muscle growth in the children with spastic CP, leading to deformity.

Several treatment options have been used to reduce the

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https://doi.org/10.1016/j.jcot.2020.01.002
0976-5662/

spasticity and to improve functions of hand and upper limb in children with CP. Intramuscular (I.M.) injection of botulinum toxin A (BTX-A) was first reported as a treatment option for focal muscle spasticity in children with cerebral palsy in the early 1990s.[5] It is a potent neurotoxin which acts by preventing the release of acetylcholine (Ach) from presynaptic axon at motor end plate. The advantage of focal BTX-A is that it directly treats the symptomatic muscle. The elimination of spastic components allows affected individuals to use limbs more effectively. The ultimate aim of BTX-A injection in children with CP is to enhance motor learning and achieve a greater functional gain through the reduction of tone in injected muscle. BTX-A treatment also has beneficial effect on ischemic muscular pains due to spasticity.

The purpose of this study was to present an objective analysis of the effect of a single intra-muscular injection of BTX-A in reduction of spasticity in the upper limb as well as functional outcome in children (4–12yrs) with spastic CP.

2. Material & methods

This prospective study was carried out from September 2016 to April 2018 at our institute after approval from the Institutional ethical committee. Children (4–12yrs) with spastic CP with unilateral or bilateral upper limb involvement, capable of maintaining a sitting posture on a chair or wheel chair with MACS (Manual Ability Classification System)[6] score 2 & above were enrolled for study. The effect of single injection of BTX-A on spasticity and function were measured as described below. Children with previous history of surgical intervention; fixed contractures; those receiving oral or intrathecal myo-relaxant drug like baclofen or anti-epileptics; with mental retardation; and those having CP other than spastic were excluded. A total of 28 children (30 upper limbs) were included in the study.

2.1. Methods

A detailed history including demographic profile, birth history, developmental history, history of any other interventions in past was taken. Physical examination including grade and type of muscle tone, any contractures or fixed deformity, range of motion and power of muscle were recorded. Modified Ashworth Scale (MAS)[7] and Modified Tardieu Scale (MTS)[8] were used to confirm and measure the spasticity in various muscle groups of each upper limb. The shoulder muscle group and hand intrinsic muscles were excluded from this scoring.

Functional outcome measurements were done by MACS score (Manual Ability Classification System) &COPM (Canadian Occupational Performance Measure) of the subjects.[9]

The target muscles which hamper the normal function and grip most were chosen for BTX-A injection on the basis of clinical examination. Muscle groups that provided significant resistance to passive range of motion, contributing to abnormal limb positioning or inhibiting function were identified for injection. The most common upper limb contracture patterns noted in CP in order of occurrence are thumb-in-palm; shoulder adduction with internal rotation; wrist flexion with forearm pronation; elbow flexion; and finger flexion.[10] Severe elbow flexor spasticity is an indication for Biceps and/or Brachialis injection. Both muscles were not injected simultaneously as suggested by various authors as it may lead to weakness of elbow flexion.[11] Biceps brachii alone is generally chosen as target muscle for elbow spasticity except in cases with severe pronation, where brachialis is injected instead, to protect supination action of biceps. The pronator teres muscle was injected for severe pronation posture with spasticity. Wrist flexion was an indication for flexor carpi ulnaris (FCU) or flexor carpi radialis (FCR) muscle injections. Predominant volar-ulnar deviation at wrist is an indication to inject FCU only. For thumb-in-palm, the adductor pollicis muscle was injected. The injection site was identified by surface anatomy as given in standard literature.[12–14] Dose for arm muscles is 2–3U/kg/muscle; for forearm muscles- 1–2U/kg/muscle; for hand muscles/adductor pollicis– a total of 0.5–1 U/Kg is given. The total dose does not exceed 8–10U/kg (or 400U) per visit, and a maximum of 50U per injection site. BTX-A 50/100 Units vials were used. Prior to injection, each 100 U vacuum dried vial is reconstituted with 1 ml sterile, preservative free 0.9% normal saline injection, USP (0.5 ml for 50 IU vial). Resulting dose units per 0.1 ml was 10 units. BTX-A was given by intramuscular route on Daycare basis. Local anaesthetic cream was applied at injection site prior to injection. The needle was aspirated to ensure that BTX-A is not injected into a vessel. One injection per muscle was used.

This was followed by targeted rehabilitation to gain maximal benefit of the BTX-A. The physiotherapy programme was started one day after injection in form of passive range of motion exercises at joints-flexion and extension at elbow, wrist and fingers; abduction and extension of thumb; and supination and pronation of forearm. Stretching exercises of spastic muscles (biceps for elbow flexion posture; pronator teres for pronation posture, adductor pollicis for thumb-in-palm posture, flexor digitorum profundus and superficialis for finger flexion posture) were started as soon as patient could allow manipulation. The physiotherapy programme was delivered 2 day/week for 2 weeks and each treatment session lasted approximately 1 h. This was followed by home based therapy by caregivers/guardians. The caregivers were taught stretching exercises and were encouraged to give home based therapy daily at least twice a day.

No casts/splints were given after the injection.

Children were evaluated pre and post injection on basis of MAS, MTS, and COPM & MACS at 3 and 6 months. Data analysis was done using SPSS version 21. Quantitative data like MACS, COPM, MAS and MTS were assessed. Mean and standard deviation were calculated and preinjection findings were compared to postinjection follow up findings using appropriate test. P value < 0.05 was considered statistically significant.

3. Results

A total of 28 children (30 upper limbs) of spastic CP with minimum follow up of 6months were available for final assessment. Study comprised 20 male and 8 female patients with mean age of 82 months (48–144months). Out of 30 limbs, 14(46.7%) had right upper limbs and 16 (53.3%) had left upper limbs involvement. Two had bilateral involvement and rest all were hemiplegics. 10 (35.7%) children were with normal birth history and 18(64.2%) children had history of premature birth or asphyxia at the time of birth. Average weight at the time of injection was 24.8 Kg.

All patients in present study had mean MACS of 2.7(range 2–3) in pre-injection period. At post-injection follow up of 3 months it was 1.5 and at 6 months 1.4. The changes in values were significant with p value < 0.05 (Table 1) The change in values of COPM at 3months and 6months were also significant with p value < 0.05. (Table 2). COPM scores at 6months were significantly lower in

Table 1
Mnnual ability classification system (MACS).

	Mean(Range)	N	Std. Deviation
MACS:BEFORE Treatment	2.70(2–3)	30	.466
PI (post injection)MACS:3 MONTH	1.53(1–2)	30	.507
PI MACS:6MONTH	1.37(1–2)	30	.490

Table 2
Canadian occupational performance measure (COPM).

	Mean(Range)	N	Std. Deviation
COPM:BEFORE Treatment	4.50(3–6)	30	.900
PI COPM:3 MONTH	5.93(4–8)	30	1.143
PI COPM:6 MONTH	6.73(4–9)	30	1.230

higher age group. Similarly, the change in values of MAS and MTS at elbow, forearm and wrist at 3months were significant with p value < 0.05 (Tables 3 and 4). Although MAS scores at all joints and MTS scores at forearm deteriorated between 3 and 6 months.

Various muscles injected are tabulated according to frequency in Table 5. Pronator teres was the most frequently injected muscle. Total dose of BTX-A given was between 50 and 180 with mean of 117.67 IU. Mean dose per Kg body weight was 4.75 IU. The injections were well tolerated by all the patients. Patients/parents reported some discomfort at injection site for first 24 h s. Four children (6 upper limbs) reported temporary decreased grip strength lasting 4–6 weeks. No other side effects were noted.

4. Discussion

Various forms of modalities for reducing tone include: physical therapy (range of motion and stretching exercises) & occupational therapy; medications like neural depressant (oral/intrathecal baclofen, Benzodiazepines, clonidine, tizanidine), neurosurgery (rhizotomies, neural transaction), orthopaedic surgery (lengthening/recession or tendon transfer) and BTX-A. Systemic antispasmodic drugs like neural depressant can be effective in diffuse spasticity and affect several muscular groups. Such systemic treatments are only partially effective in reducing spasticity. They are often associated with intolerable side effects including dizziness, sedation, confusion, nausea, vomiting, lowers seizure threshold and CNS depression. Surgical interventions have variable efficacy, significant morbidity and are irreversible. Literature support for surgical intervention for the upper limb in CP is largely derived from retrospective or descriptive studies. There are no randomized trials comparing surgical outcome with controls.[15,16]

Although literature has established the role of BTX-A injections for lower limb spasticity in patients with cerebral palsy,[17,18] there is paucity of studies for its effect on upper limb spasticity and functional outcomes. Among several practical issues with upper limb BTX-A, most important are-optimal timing & dosing of BTX-A and selection & localization of target muscles. In present research we studied effects of BTX-A in treatment of upper limb spasticity in cerebral palsy. 93% cases in this study were Hemiplegics.

Manual localization techniques for BTX-A provided promising functional results[19,20] Some authors suggested electrical stimulation[11] or ultrasound guidance[21] to be more accurate in needle placement. Park et al. in their literature review found no difference in method of localization of target muscle.[22]

The mean total dose of BTX-A was 117.67 IU and mean dose per Kg body weight was 4.75 IU. The total dose and per kg BTX-A used in our study is less compared to Wallen et al., 2004 & Yang et al., 2003. This could be because of low average body weight as well as less frequency of arm muscles injected compared to forearm muscles & adductor pollicis in our study group. The literature describes various dilution volumes for BTX-A ranging from 0.5 ml to 5 ml for 100 IU. We used 0.1 ml saline containing 10 IU of Inj. BTX-A. Lowe et al., suggest low dose high concentration to be used.[23] These authors used 0.1 ml saline containing 20 IU of Inj. BTX-A. Future research is required in different dose regimens.

This study supports previous study findings on BTX-A effects on upper limbs for children with CP.[11,19,24,25] There was significant decrease in spasticity at arm, forearm& wrist levels with significant decrease in MAS and MTS at 3 months after the injection. However, MAS & MTS increased at 6months post injection. This trend shows that effect of Botulinum weans off after 3months with return of local spasticity.[11,19,20] Wallen et al. also reported similar pattern of spasticity.[11] These authors reported sustained functional outcomes after botulinum toxin injections despite return of local spasticity. In present study, we also noticed significant improvement in MACS and COPM at 6 months despite return of local spasticity. Also, COPM scores were significantly lower as the age of child increased. This may suggest that BTX-A may have more beneficial effect in younger age group.

In present study we did not use casting post injection. However, we utilized dedicated physical therapy program for each case. Lowe et al.[23] reported that group receiving BTX-A followed by therapy had greater 1-month and 3-month gains in upper limb quality of movement, function, and spasticity, and greater 6-month gains in function. We also observed similar pattern that overall function keeps on improving beyond 3months, although spasticity may return slowly. Published large systemic reviews[26–28] agree on the finding that PT alone may be beneficial and BTX-A provides a supplementary effect to enhance upper limb(UL) and individualized outcomes. All children received a prolonged course of rehabilitation therapy. We acknowledge the fact that this in itself might have led to some benefit in children.[28]

Literature describes various scoring methods including video based scoring systems for UL CP.[29] We utilized MAS & MTS as a measure of spasticity as these are applied manually to determine the spasticity, need no special equipment and are easy to use. But these scales are observer dependent and there may be inter-observer and intra-observer differences while using these scales.(R) This may be a drawback of using these scales.

Functional score like COPM records the patient's care giver's perception of subject's occupational performance. It is a semi structured patient and caregiver directed interview that guides the subject in identifying problem areas in the domains of self care, productivity and leisure. (R) COPM is an individualized measure designed to reflect the goals of individual clients and takes into account their roles and the environment they live.

Table 3
Elbow, forearm and wrist Modified Ashworth Scale score (MAS).

		Mean	N	Std. Deviation
ELBOW	MAS ELBOW:BEFORE Treatment	1.817	30	.6884
	PI MAS ELBOW:3MONTH	.550	30	.7352
	PI MAS ELBOW:6MONTH	.633	30	.5862
FOREARM PRONATOR	MAS PRONATOR TERES:BEFORE TT	2.650	30	.5111
	PI MAS PT:3MONTH	.917	30	.5266
	PI MAS PT:6MONTH	1.350	30	.3511
WRIST	MAS WRIST:BEFORE Treatment	2.250	30	.8174
	PI MAS WRIST:3MONTH	.883	30	.5676
	PI MAS WRIST:6MONTH	1.017	30	.6086

Table 4
Elbow, forearm and wrist Modified Tardieu Scale score (MTS).

		Mean	N	Std. Deviation
MTS ELBOW	BEFORE Treatment	48.33	30	35.045
	PI: 3MONTH	8.33	30	16.626
	PI:6MONTH	2.50	30	5.981
MTS FOREARM PRONATOR	BEFORE Treatment	8.33	30	16.626
	PI:3MONTH	4.83	30	4.044
	PI:6MONTH	9.43	30	5.151
MTS WRIST	BEFORE Treatment	44.33	30	25.418
	PI:3MONTH	7.33	30	9.260
	PI:6MONTH	6.00	30	5.318

Table 5
List of muscles injected.

Muscles	Frequency
Pronator Teres	28
FCU	19
Adductor Pollicis	19
FCR	11
Brachialis	9
Biceps	8

As children younger than 8 years have difficulty with the self-assessment and interview, proxies are necessary. The parents are asked to fill in COPM scores in such cases. One caution in the use of COPM for group comparisons is necessary because the identified problems are individualized.

On the other hand MACS is a caregiver report system that describes how children with CP use their hands to handle objects in daily living activities. The score is designed to reflect the child's typical performance in everyday like situation.

We found these scores easy to use, less time consuming & easily adjusted to needs in Indian scenarios. More Research is needed in future towards developing a scoring system for UL CP which fulfills the need of an ideal scoring system.

Four children (6 upper limbs) reported temporary decreased grip strength lasting 4–6 weeks but normalized at 3 & 6 months' evaluation after injection. Other authors also found a similar pattern of response for muscle tone.[11,19,20] No other complication or side effect of BTX-A was noted in this study.

Koman et al.[30] in their randomized placebo controlled study concluded that Children receiving BTX-A injections demonstrated short term improvements in upper extremity function. However, the majority of study participants underwent 3 injection sessions over 6 months rather than the 1-injection session common in other studies. Olesch et al.[31] in a RCT concluded that repeat BTX-A injections combined with OT resulted in progressively reduced spasticity and improved parental perception of performance. Further research is warranted regarding frequency and total sessions of BTX-A for optimal outcome in UL CP.

Cost of BTX-A will remain an important factor to consider in management of spasticity in CP. Literature describes significant reduction in surgery and the use of healthcare resources during the first year following treatment.[32,33] However, further research is needed regarding how it will affect the future need for surgery and associated outcomes.

Limitations of this study include that there was no control group and lack of double blinding for therapists & caregiver. Also, functional outcome has been assessed at 3 and 6 months post injection with short follow up.

To conclude, our study supports use of BTX-A along with physical therapy program for management of UL CP. Randomized control trials with long follow up are required in future with special focus on dosing and timing, scoring system for functional outcome as per regional needs and issue for antibody formation for repeat injections of BTX-A.

Source of support

None.

Declaration of competing interest

None.

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