Botulinum Toxin Type A for Treatment of Children with Spastic Cerebral Palsy

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Abstract

Objectives: To evaluate safety and effectiveness of Botulinum Neurotoxin A in the treatment of children with spastic cerebral palsy.

PATIENTS AND METHOD: Hundred children with spastic cerebral palsy, age from 1-14 years, studied from 1st Oct. 2008 to 1st Oct. 2009. All patients with dynamic deformities received Botulinum Neurotoxin/A injections as a part of rehabilitation program; they were assessed clinically by special parameter for effect of Botulinum Neurotoxin.

Results: The peak effect was noticed after 2-3 weeks in the majority of patients, the effect lasted for 3-10 months; most of children experience significant improvements in ambulatory status, MAS, PRS, TAS and GAS scores, the improvement of statistical significance, $P < 0.05$. Patients' functional status was improved, no serious side effect detected except mild transient pain at injection site and flue like illness in few patients.

Conclusions: The treatment by Botulinum Neurotoxin/A is safe and effective and produces a sustained structural modification of the lower limb. It is useful as adjunctive therapy as complementary to stretching exercises and orthotics therapy to ameliorating spasticity in children with cerebral palsy especially for the younger children.

Key words: Botulinum Neurotoxin, cerebral palsy

Abbreviations: cp = cerebral palsy, BoNT = Botulinum Neurotoxin, MAS = Modified Aschworth Scale, PRS = physician rating scale, TAS = thigh adductor scale and GAS = Goal attaining Scale.

Introduction

Cerebral palsy is one of the most common congenital or acquired neurological conditions in children. Manifestations of the disease are primarily motor with or without mental or developmental deficits; cp doesn't constitute a single clinical image, but a total of symptoms.[1] Cerebral palsy is a group of disorders caused by a non progressive injury to the developing central nervous system (CNS) in children younger than 3 years, resulting in neurological and musculoskeletal abnormalities.[2] The overall prevalence of cerebral palsy is 1.5-2.0/1000 of live births.[3] Spasticity, contracted muscles, in children with cp is a serious problem that affects daily life activities, use of path and achieving the rehabilitation goal. Stiffness, restricted movement, is responsible for the development of contractures and serious joint complications, stiffness usually affecting muscles with spasticity.[4]

Effective therapeutic management of cp should be specifically directed to improve the neurological and motor impairments affecting the individual patient and will most often require the efforts of multidisciplinary health care professional team administering physical, pharmacological, and surgical treatments.[5] Traditionally, there has been a much greater highlighting on treatment of muscular hypertonic symptoms than weakness and lack of selective motor control; moreover the muscles hypertonia and weakness symptoms may determine the level of disability and long-term prognosis of children with cp.[6]

Chemodenervating agents such as phenol, alcohol and BoNT-A become an important part of effective treatment regimen specifically for focal spasticity or dystonia associated with cp. Treatment with chemodenervating agents are not effective in treating of spasticity or dystonia in disorders such as cerebral palsy but it designed to ameliorate the symptoms of motor dysfunction. [7]

Treatment with Botulinum toxin-A become a main way of treatment for children with spastic cerebral palsy. [8] The use of BoNT/A to treat spasticity in children with cp has increased rapidly despite limited knowledge of long-term effectiveness of early intervention.[9] Botulinum toxin -A- was considered safe and effective when used in therapeutic doses;[10] the adverse systemic effects are rare, and may include flu like signs, transient fatigue and nausea.[11]

Botulinum toxin-A was well known as a causative agent of food poisoning and infant botulism; it is a potent neurotoxins produced by the bacteria *clostridium botulinum* under anaerobic conditions. The BoNT binds to cholinergic nerve endings and inhibits release of the neurotransmitter acetylcholine by blocking the binding of acetylcholine vesicles to the anterior of the motor end plate plasma membrane; it takes about three months for original nerve ending to be restored, thus, the effect of BoNT pharmacologically as well as clinically completely reversible. [12]

Children receive higher doses per kilogram of body weight than adults and they could be more susceptible to developing systemic effects than adult; subclinical effects of BoNT on neuromuscular transmission distant from the site of injection were reported, as evidenced by increased jitters, increase fiber density, and occasional blocks on single fiber electromyogram.[13] There is also no evidence of central nervous system effect after intramuscular injection of the toxin; however BoNT therapy can have extended effects on the

motor system. Re-injection should not be done within less than 12 weeks because more frequent injection are more likely to give rise to antibodies and a non-linear dose-response relationship is to be expected. [14] Although the effect of BoNT/A are seen primarily in a reduction of hypertonia, the change in tonus can improve the child's balance strength, motor control and fixed contracture. [15] As the child develops, the spastic muscles fail to grow as quickly as the neighboring structure, and dynamic structures are transformed into fixed contractures; so relaxation of spastic muscles allows it to stretch, encourages their growth and prevent contractures. These improvements will lead to functional gain. [16] The Physiological and mechanical effect of BoNT/A treatment are genuine and measurable in patient with spastic diplegia. However, these effects might not trigger a major changes in function or change in the patient parent's perception of function and thus not be recorded as a significant improvement in the patient's family and social life. [17]

Clinical assessment and follow up

The assessment of patients consisted of:

1-Parental notes and reports whether there was improvement, time of onset of improvement, peak effect of action and side effect.

2-Clinical, neurological and physiotherapy assessment.

3-Ambulatory status: Compare of the ambulatory status before and after inject according to the following categories: [18]

A-Non ambulatory, unable to walk with or without assistance.

B-Nonfunctional ambulatories can walk with assistance or supervision.

C-Functional ambulatories can walk independently indoors with or without aids.

D-Community ambulatories can walk indoors and outdoors at all times.

1-Modified Ashworth Spasticity (MAS) scale; local efficacy is evaluated according to the muscle tone [19]

A-Normal

B-Mild, slight increase in muscle tone, "catch" in limb movement or minimal resistance of movement through less than half of the range.

C-Moderate, marked increase in muscle tone through most of the range of motion, but the passive movement of the affected part is easily performed.

D-Severe or prominent increase in muscle tone with difficulty in passive movement.

E-Extreme, affected part is rigid in flexion and extension.

2-Physician Rating Scale (PRS): This scale allows six functional elements of gait to be assessed while the patient is walking barefoot for a distance of at least 15 steps. This scale grades the following functional elements. [19]

A-Gait pattern (0 – 2)

B-Position of the ankle while walking (0 – 2)

C-Elevation and curvature of the foot while walking (0 – 3)

D-Position of the knee while walking (0 – 3)

E-Degree of flexion and shortening of the lower limbs (0 – 3)

F-Gait speed (0 – 1)

The total PRS was the sum of the six components for each patient (0-14), the score 0 is the worst and 14 is the best score)

3-Spasticity scale for thigh adductor (TAS)[20] this scale be as score according to the examination of spasticity of adductor movement.

0 = Normal muscle tonus

1 = Increase tonus, thigh easily abducted up to 45º by only one examiner

2 = Thighs abducted up to 45º by only one examiner

3 = Thighs abducted up to 45º by only one examiner with moderate effort

4 = Two examiner needed to abduct thigh up to 45º

4-Goal attainment scale (GAS): provides the means to establish therapy goals and grade the therapeutic results attained in a standardized fashion, it is a simple and reliable method that can greatly assist the overall evaluation of therapeutic outcome. [14] The scale was arranged as following scores:

- 2= No change of the child initial condition.

-1= Slight improvement, but below the defined goal.

0 = Attains the defined therapeutic goal.

+1= Improvement slightly exceed the defined therapeutic goal.

+2= Improvement clearly exceed the defined therapeutic goal.

Physiotherapy program was continued for all patients throughout the study prior to the use of botulinum toxin, at least for one hour three times sessions.

Objectives

The study was designed and performed to evaluate the safety and effectiveness of Botulinum toxin in treatment of children with spastic cerebral palsy.

Patients & Methods

Design and setting

A descriptive clinical trial on 100 children with spastic cerebral palsy managed in Neurosciences Hospital for BoNT inject, during period 1st Oct. 2008 to 1st Oct. 2009.

All patients and their families were informed about the aim and suspected benefit of the study

before obtaining their agreements for participation according to the medical research and ethical regulations, thus an oral consent was taken from all enrolled participants and their families.

All the medical research ethics rules and instructions regarding patient's privacy, humanity and security; as well as the medical research, laboratory data and investigation results were strictly considered throughout all the steps of study.

The inclusion criteria

1-Children from 1 to 14 years of age.
2-Patients with dynamic deformities of the lower limbs were considered to be those in which the limb could return to the neutral position with maximal or sub maximal manipulation.
3-Patient taking part in rehabilitation programs.
4-There was no difference between the severity of the functional deficit between the right and left lower limbs.

The exclusion criteria

1-Fixed deformity of a joint.
2-Prior orthopedic surgery or the need for surgical treatment.
3-Use of aminoglycoside antibiotics.
4-Discontinuation of physiotherapy.
5-Refuse to participate or give consent by patients or their families.

Clinical assessment and follow up

Patients were assessed on admission and after 30, 90 and 180 days from the injection have been started. Diagnosis of all patients confirmed to have spastic cp in Pediatric Neurology Clinic/Neurosciences Hospital by clinical examination, neuroimaging, biochemical and hematological laboratory investigations when needed; then assessed by at least one physiotherapist before being included in the study. Clinical assessment done during the study depending on the assessment of parent reports, neurological examination, ambulatory status of patients, Modified Ashworth Spasticity (MAS) scale, Goal attainment scale, Physician Rating Scale (PRS) and Spasticity scale for thigh adductor (TAS).

Treatment (intervention)

All treatments received by patients prior to the study were continued; patients did not receive any surgical intervention during the study.

All the patients received BoNT/A therapy (Botox ®, Allergan); the lyophilized preparation of the toxin (I flask = 100 U = 5 ng) was stored at 2ºc - 8ºc and reconstituted with sterile normal saline on bases of needs at the time of injection. The maximum doses of BoNT/A was 12 U/kg body weight as 3-6 U/kg for large muscle and 1-2 U/kg for small muscle as 50 U per each injection point; [15] number of injection points and the dose adjusted for each muscle. In general the doses of BoNT was calculated and injected after sedating children by 5% chloral hydrate elixir. After the muscle was injected the parents were adviced to casting the ankle foot for 3 weeks. **(Details in table-1)**

Statistical analysis and reporting of obtained data were carried out by using Microsoft Excel - Windows XP professional program. Statistical tests were performed using a null hypothesis of no difference with a two-tails paired student t-test and Chi test; the level of significance of P value was ≤ 0.05, of high significance was $\leq 0.01$and of very high significance was ≤ 0.001.

Table 1: Pediatric doses of botulinum toxin A (Botox 2 Allergan)

	Muscle	Dose (U/Kg)	No. of injection
Hip	Iliopsoas	1-2	2
	Rectus femoris	3-4	2
Knee flexion	Middle biceps femoris	3-6	3-4
	Lateral biceps femoris	2-3	1-2
Thigh adducted	Adductor longus and brevis	3-6	1-2
Knee extended	Quadriceps	3-6	4
Equinovarus	Medial and lateral gastrocnemius	3-6	1-2
	Soleus	2-3	1-2
	Tibialis posterior	2-3	1
	Tibialis Anterior	1-2	1
	Flexor digitorum brevis	1-2	1
	Flexor digitorum longus	1-2	1
	Flexor hallucis longus	1-2	1
Hallux extended	Extensor hallucis longus	1-2	1

Results:

The enrolled children female/male ratio was 1/ 2.062; with age 43.86±21.99 months; their body weight range 8-28 kg. All patients had equines in both feet and scissoring they were injected with BoNT/A in the gastronomies, soleus muscles and adductor muscle groups. The parent reported that the medication started having an effect between the second and third week after application.

Ambulatory state

Although the differences before and after BoNT/A injection were insignificant statistically, P

> 0.05, but treatment improved the ambulatory state of patients, twenty eight non-ambulatory patients (75.6%) improved to become nonfunctional ambulatories and 9 (24.3%) not improved; eighteen (60.0%) of non-functional ambulatories improved to be functional ambulatories and 12 (40.0%) did not improved; fifteen (46.9%) of functional ambulatory improved to be community ambulatories and 17 (53.1%) did not improved. (**Table-2, 3 and Fig-1**)

Table- 2: Clinical assessment parameters of patients before and after BoNT injection.

Clinical assessment parameters	Before	After	T-test, P value
Ambulatory state	1.97±0.85	2.57±0.85	> 0.05
Modified Ashworth Spasticity scale (MAS)	3.95±0.70	2.22±0.95	< 0.005
Physician rating scale (PRS)	7.34±1.69	10.31±2.19	< 0.05
Thigh adductor scale (TAS)	3.18±0.83	1.37±0.66	< 0.005

Table- 3: Assessment of ambulatory state of participants before and after BoNT injection.

Ambulatory state	Before BoNT injection (n)	After BoNT injection (n) (%)			
		Non-Ambulatory	Nonfunctional ambulatories	Functional ambulatories	Community ambulatories
Non-Ambulatory	37	9 (24.3%)	28 (75.6%)	-	-
Nonfunctional ambulatories	30	-	12 (40.0%)	18 (60.0%)	-
Functional ambulatories	32	-	-	17 (53.1%)	15 (46.9%)
Community ambulatories	1	-	-	-	1 (100%)

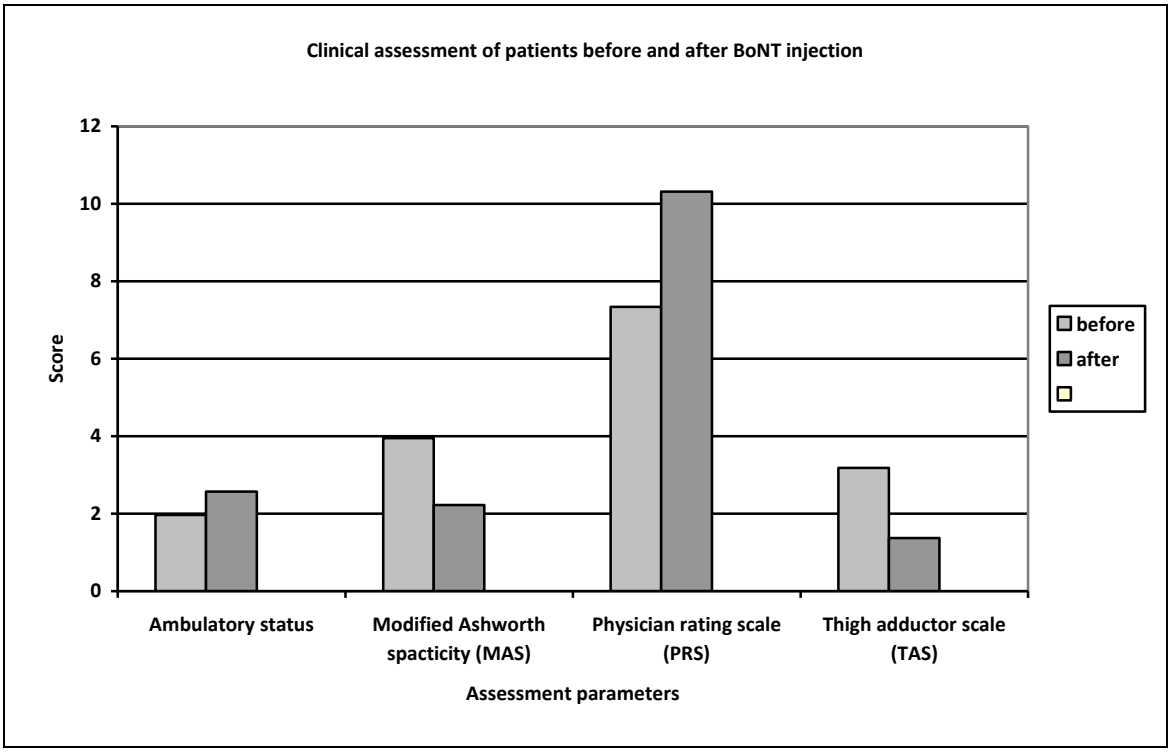

Figure- 1: Clinical assessment parameters of patients before and after BoNT injection.

Modified Ashworth Spasticity scale (MAS)

There was obvious decrease in the spasticity score after BoNT injection, differences before and after BoNT/A injection were of high statistical significance, P < 0.005; patients of moderate, severe increased muscle tone and extreme rigidity groups as following the moderate (marked) increase muscle tone group gained reduction in muscle tone to the mild and normal by 77.8% and 22.2% respectively; among the severe increased muscle tone group reduction was to mild and moderate by 83.8% and 12.9% respectively; also the extreme increased muscle tone group (rigidity) was gained reduction in muscle tone to the mild and moderate muscle tone by 44.4% for both. While both groups the normal and mild increased muscle tone did not gained any reduction in the

muscle tone after BoNT injection. **(Table-2, 4 and Fig-1)**

Physician rating scale (PRS)

Assessment done by physician showed obvious improvement in the PRS score of both lower limbs, differences before and after BoNT/A injection were statistically significant, $P < 0.05$; among the 39 patients who assessed before and after the BoNT injection. (**Table-2, 5 and Fig-1)**

Table- 4: Assessment of Modified Ashworth Spasticity scale (MAS) of participants before and after BoNT injection.

Modified Ashworth Spasticity scale (MAS)	Before BoNT injection (n)	After BoNT injection (n) (%)				
		normal	Mild increase in muscle tone	Moderate increase in muscle tone	Sever increase in muscle tone	Extreme (rigid)
normal	-	-	-	-	-	-
Mild increase in muscle tone	2	2 (100%)	-	-	-	-
Moderate increase in muscle tone	18	4 (22.2%)	14 (77.8%)	-	-	-
sever increase in muscle tone	62	1 (1.6%)	52 (83.8%)	8 (12.9%)	1 (1.6%)	-
Extreme (rigid)	18	1 (5.5%)	8 (44.4%)	8 (44.4%)	1 (5.5%)	-

Table- 5: Assessment of Physician rating scale (PRS) of participants before and after BoNT injection.

Physician rating scale (PRS)	Before BoNT injection (n)	After BoNT injection (n) (%)					
		Score (8)	Score (9)	Score (10)	Score (11)	Score (12)	Score (13)
Score (5)	4	1 (25%)	2 (50%)	1 (25%)	-	-	-
Score (6)	10	1 (10%)	3 (30%)	6 (60%)	-	-	-
Score (7)	7	-	2 (28.5%)	5 (71.5%)	-	-	-
Score (8)	11	-	-	3 (27.3%)	-	6 (45.5%)	2 (18.2%)
Score (9)	3	-	-	-	-	3(100%)	-
Score (10)	4	-	-	-	-	-	4 (100%)

Thigh adductor scale (TAS)

The group of adductor muscles was significantly respond to treatment with BoNT injection, $P < 0.005$; the TAS scores obtained after injection showed clearly the improvement in functions of adductor muscle of both lower limbs. (Table-2, 6 and Fig-1)

Goal attainment scaling (GAS)

Assessment of goals attained by the therapeutic procedure after BoNT injection showed that patient got benefit from the procedure with scores 0, +1 and +2 were 38%, 51% and 8% respectively; while those who did not got benefit from therapeutic procedure with scores – 1 and – 2 were 2% and 1% respectively. (Fig-2)

Side effects

No serious side effect had been reported among 82% of patients, mild pain at the site of injection 11% and flue like illness in 7%. (**Fig-3)**

Table- 6: Assessment of Thigh adductor scale (TAS) of participants before and after BoNT injection.

Physician rating scale (PRS)	Before BoNT injection (n)	After BoNT injection (n) (%)					
		Score (0)	Score (1)	Score (2)	Score (3)	Score (4)	Score (5)
Score (0)	2	2 (100%)	-	-	-	-	-
Score (1)	1	-	1 (100%)	-	-	-	-
Score (2)	11	4 (36.3%)	7 (63.7%)	-	-	-	-
Score (3)	50	-	39 (78.0%)	10 (20.0%)	1 (2.0%)	-	-
Score (4)	35	-	6 (17.1%)	28 (80.0%)	1 (2.9%)	-	-
Score (5)	1	-	-	1 (100%)	-	-	-

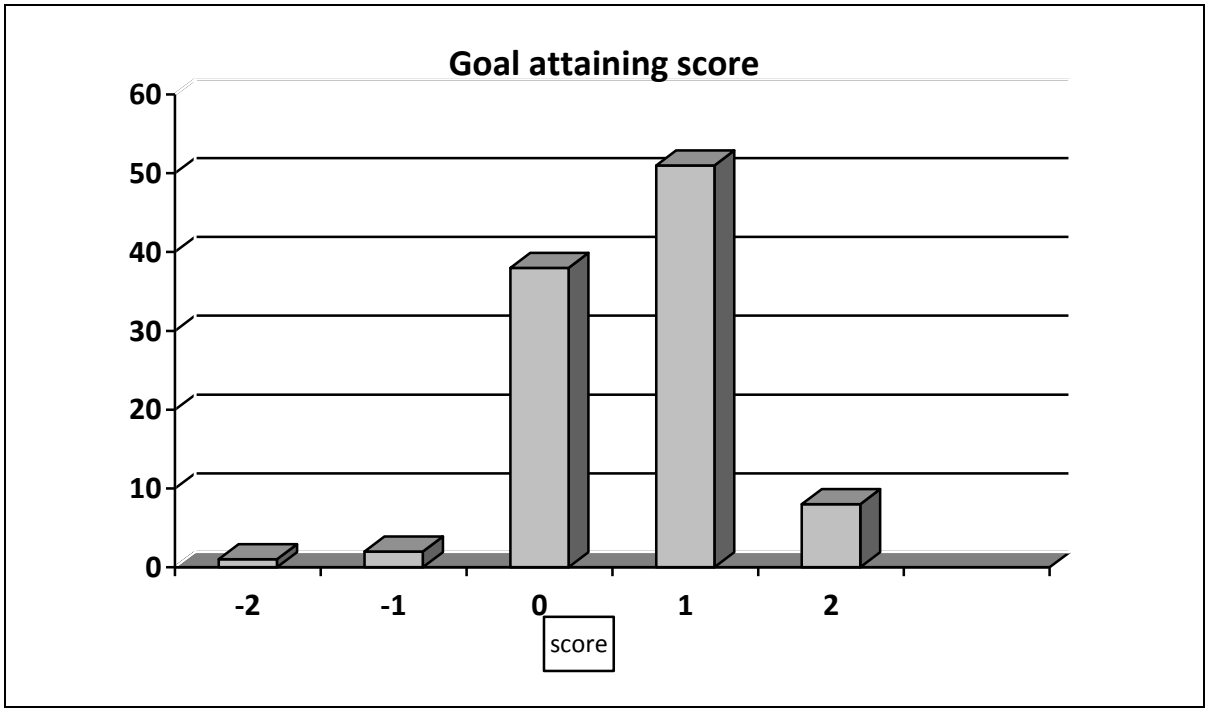

Figure- 2: Goal attaining score obtained after BoNT injection.

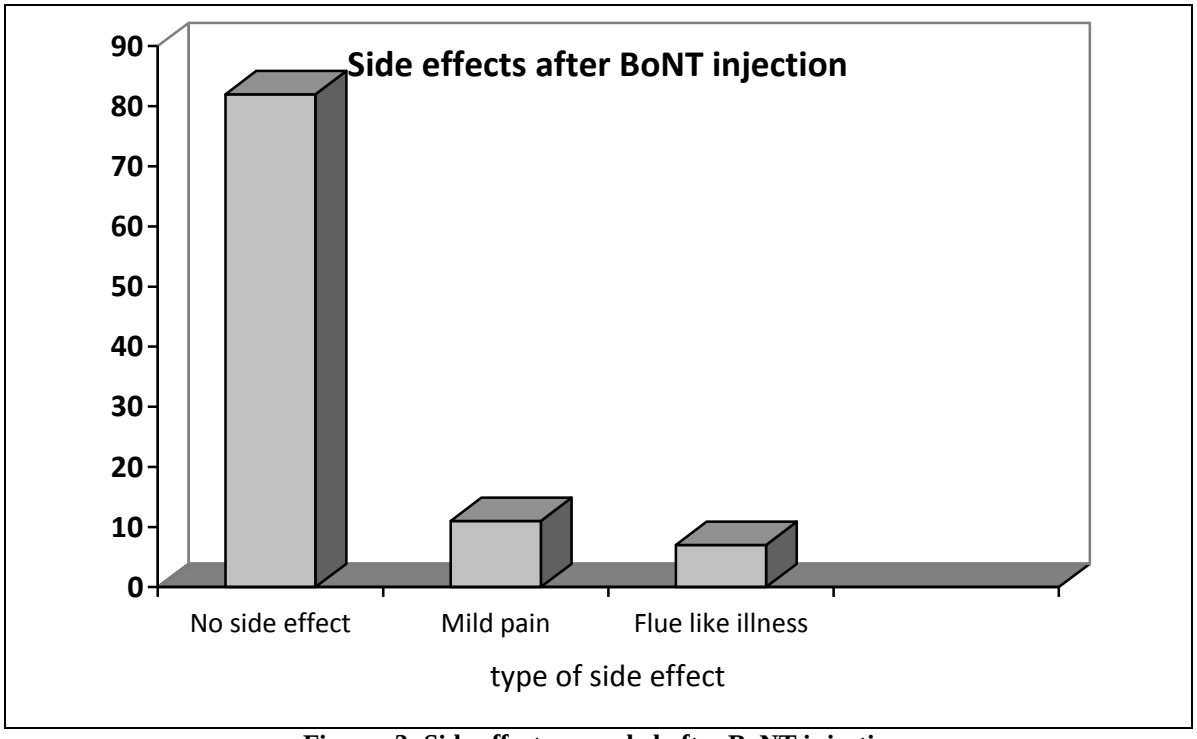

Figure- 3: Side effects recorded after BoNT injection.

Discussion:

Botulinum toxin blocks neuromuscular conduction by binding to receptor sites on motor never terminals, entering the nerve terminals and inhibiting the release of acetylcholine. The nerve can sprout and re-enervate the muscle and thus weakness is reversible. [19] When treating children with spasticity, one must be aware that the negative effect of spasticity also creates problems in cp such as weakness and poor posture control; Thus, careful judgment should done between the effect of BoNT in alleviating the spasticity and the possibility of poor response which might be due to other factors and the unmask contractures in severe degrees of spasticity. The use of BoNT to decrease spasticity of the agonist muscles can be facilitated to improve the function of previously weakened antagonist muscles; this will lead to restoring muscle balance across joints, by this way joint contracture or fixed joint deformities can be prevented. The children

can also be tuned to a specific and targeted motor skill, with continuing active and passive muscle stretching. From present study we found that by decreasing the spasticity of the gastronomies muscle, the range of active or passive movement across both the knee and ankle joints are improved.

From observations, we noticed that effect of BoNT started 2-3 weeks after injection and lasted 3-10 months, just about the same results obtained by Carlos study and late to the findings of Virginia wong study; majority of the child's parents reported a dramatic improvement in the tone of the lower limb, similarly to what reported by above two studies. [20, 21, 22]

Treatment with BoNT/A improved ambulation, there were 28(75.6%) non ambulatory children become non-functional ambulatory, 18(60.0%) non functional children become functional and 15(46.9%) of the functional ambulatory children become community ambulatory.

Positioning of feet was improved due to reduction in spasticity of the calf muscles which measured by the modified Ashworth scale (MAS); Physiological explanations for this adjustment in the feet including not only weakness of the gastronomies and soleus, but also the increase in length of the gastronomies muscle-tendon unit. Any of these effects could be the direct result of chemical denervation caused by BoNT/A which is unlikely to that may occur spontaneously. [23]

Also BoNT improve equines gait pattern significantly in children with spastic cp when these parameters were assessed using PRS and coincide with studies of Virginia wang and Duchen. [18, 22] (Table-4)

A clear improvement in the spasticity of the thigh adductor muscles (TAS) was also observed after treatment with BoNT/A, corroborating the findings of Hanzeuci study.[24] The positive effect on the thigh adductor muscles was progressive and was sustained throughout the follow up period.

Most of the patients attained or slightly exceed the defined therapeutic goals; it has been stressed recently that assessment of functional improvement is more important than assessment of the reduction in muscle tonus or the increase in the range of motion of the joint. The outcome of BoNT/A effects on children was different from that on adults whose organs are relatively static; because children have two processes that are exclusive to childhood growth and development which superimposed on the underlying spastic condition.

However, we tried to assess the efficacy of BoNT/A applied in a single session; serial injections of BoNT/A may lead to a greater reduction in focal spasticity and allow children with cp to learn movement pattern that more closely resemble normal ones and to improve their balance and gait speed as well as increase step size when ambulating. [19] In addition to increased functional capacity, another important benefit of long-term treatment with BoNT/A is that surgical interventions can be postponed. [15]

Family members must have realistic expectations about the BoNT/A before the procedure started; Bjornson [17] stated that the family members' expectations from therapy had to remove from actual effects of the treatment because they had difficulty in appreciating the benefits of the treatment.

The BoNT/A treatment were generally well tolerated and safe when used to treat spastic cp and rarely produce serious side effects. Concurrently the literature review stated that no important side effects were observed after treatment by BoNT, the same what we found in our trial; however we did observe flue like illness or complaining of mild pain and/or tenderness at the side of injection in few cases.

The treatment by BoNT/A is safe and effective and produces a sustained structural modification of the lower limb. It is useful as adjunctive therapy as complementary to stretching exercises and orthotics therapy to ameliorating spasticity in children with cerebral palsy especially for the younger children.

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