

Original Article

Our Experience with Intramuscular Injections of Botulinum Toxin A for the Treatment of Upper Limb Flexors Spasticity after Stroke

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ABSTRACT

Background: Focal spasticity can be a major drawback in the rehabilitation of stroke patients. Previous studies suggest a beneficial effect of Botulinum toxin A (Botox A) for relief of spasticity.

Objective: To evaluate the therapeutic effects of intramuscular injections of Botox A (Btx A) on spasticity of the upper limb.

Design: An open-label non-controlled trial for a duration of 16 weeks was design to determine the efficacy and safety of intramuscular Btx A injections in the treatment of 56 patients with spastic hemiparesis after stroke. The patients were assessed at baseline, 2, 4, 12 and 16 weeks after treatment by several outcome measures – modified Ashworth scale, motricity index arm score, limb position at rest, semi-quantitative

ordinal scale for severity of pain, patient's global response to Btx A treatment, Barthel index of activities of daily living, difficulties encountered during three upper limb motor tasks.

Results: Significant reduction of muscle tone, spasticity related pain and improvement in the three selected functional tasks (cleaning the palm of the affected hand, cutting the fingernails of the affected hand, putting the affected arm into the sleeve) were observed one week after Btx A injections and were sustained throughout the 16 weeks follow-up period.

Conclusion: Botox A is effective and safe adjunctive treatment to on-going rehabilitation for patients with post-stroke localized moderate-to-severe spasticity refractory to physical and medical treatments.

KEYWORDS: Botulinum toxin A, spasticity, stroke

INTRODUCTION

Severe hypertonia of upper limb muscles is a common complication in patients with stroke. Only a very small minority of these patients regain useful function of the paralyzed arm^[1] and the prospects of recovery after the first three months of the stroke are usually negligible^[2]. Spasticity is classically defined as a velocity-dependent increase of tonic stretch reflexes (muscle tone) with exaggerated tendon jerks^[3]. It is one of the positive features of the upper motor neuron syndrome. Clinically, hemiplegic patients demonstrate anti-gravity postural pattern of spasticity involving extensors muscles in the lower limb and flexors muscles in the upper limb with adducted (internally related shoulder), flexed elbow, pronated forearm, bent wrist, clenched fist and thumb with palm deformity. Although muscle weakness and loss of dexterity are important factors in the motor functional disability of these patients, the contribution of muscle spasticity is often quite significant. Spasticity may interfere with voluntary motor function in patients with residual muscle power^[4]. In addition it frequently causes difficulties with activities of daily living, and pain and discomfort in the affected limb.

The mainstay of treatment of spasticity remains the physical therapy (therapeutic exercises, positioning, stretching, adjunctive modalities such as cold, heat, ultrasound, electrical stimulations), but moderate to severe spasticity often responds only partially. Systemic anti-spasticity drugs are non selective in their action and may result in generalized weakness and sedation^[5]. Surgical procedures e.g., rhizotomies, myelotomies, neural transection, tendon transplant and lengthening^[6] have variable efficacy, significant morbidity and are irreversible.

An alternative strategy in the management of muscle spasticity is chemical neurolysis. However nerve blocks and motor points injections in the upper limb with phenol and alcohol may cause skin sensory loss and dysaesthesia and their effect often diminishes with repeated treatment^[7]. In recent years, Botulinum toxin type A (Btx A) has shown to be an effective antispasticity agent^[8-10]. When injected directly into the muscle, it produces reversible, partial chemical denervation by preventing the release of acetylcholine from the pre-synaptic axon at motor endplate^[11].

Although a number of studies demonstrated that Botulinum toxin A decreases muscle tone in

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spastic muscles^[9,12-17], only two controlled studies had shown functional improvement in the use of the limb with this therapy^[15-16]. Few studies have focused on pain relief as an additional benefit of local Btx A spasticity treatment^[17-19].

The aim of the present open study was to evaluate the efficacy of Botulinum toxin A for the treatment of chronic limb flexor spasticity in stroke patients.

SUBJECTS AND METHODS

Patients with hemiplegic stroke were recruited from the outpatient clinic for neuro-rehabilitation at Physical Medicine and Rehabilitation Hospital at least six months after the onset of the cerebrovascular event. They were treated in the spasticity clinic at the same hospital for the period January 2001 to September 2002 after providing written informed consent to participation. Prior to their admission to the study all participants have been trained intensively in patient rehabilitation program and outpatient rehabilitation courses in the same hospital.

Entry criteria were chronic moderate-to-severe spasticity in the flexor muscles in the upper limb, motor tone score ≥ 2 on the Modified Ashworth scale (MAS)^[20], refractory to conventional physical and medical treatments, with static or slowly progressing course, and localized in specific target muscles enabling practical treatment by local injections.

Exclusion criteria were fixed contractions of target muscles, neuromuscular diseases or other chronic diseases (rheumatoid disease) causing major physical disability in the target region, previous treatment with Botox A, neurolytic or surgical procedures in the study limb.

Patients were required to maintain ongoing spasticity treatment (medication, physical therapy). De novo treatment with spasmolytic drugs was not allowed. One and the same physiatrist following standardized protocol assessed each patient. Follow-up assessments were scheduled at two weeks and 1, 3, 4 months after injections with Botulinum toxin A. The following outcome measures were used: Modified Ashworth scale for measurement of spasticity (Table 1), mobility index^[21] for measurement of motor control at shoulder elbow and hand, semi quantitative ordinal scale for measurement of severity of pain in the target muscles (1 = absence of pain, 2 = light pain, 3 = moderate pain and 4 = severe pain), patient's global response to BtxA treatment (Table 2)^[19], Barthel index (BI) for functional assessment of activities of daily living.

The limb position at rest was tested for the elbow and wrist in degrees of flexion from neutral position. Five-step scale (0 = hand closed, 1 = one quarter open, 2 = one half open, 3 = three quarters open and 4 = fully open) was used to test rest position in

Table 1

Table 1: Modified Ashworth Scale

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 range of motion (ROM) when the part is moved in flexion or extension/abduction or adduction, etc.
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 the affected part is easily moved
3	Considerable increase in muscle tone, passive movement is difficult
4	Affected part is rigid in flexion or extension (abduction or adduction, etc.)

Table 2

Patient Evaluation of Global Response to Botulinum Toxin A Treatment

-4	Marked worsening in severity of pain and function
-3	Moderate worsening in severity of pain resulting in a decline in function
-2	Moderate worsening in severity of pain, but no change in function
-1	Mild worsening in severity of pain, but no change in function
0	No effect
+1	Mild improvement in severity of pain, but no change in function
+2	Moderate improvement in severity of pain, but no change in function
+3	Moderate improvement in severity of pain resulting in a functional improvement
+4	Marked improvement in severity of pain and in function

metacarpophalanges and interphalangeal joints of fingers.

Patients and caregivers were also asked to score the difficulties encountered in performing functional activities that often result from upper limb spasticity: 1 = being able to put the affected arm through the sleeve, 2 = being able to open the hand of the affected limb for cleaning the palm, 3 = being able to open the hand of the affected limb for cutting the fingernails.

The difficulty was graded as follows: no difficulties, little difficulty, moderate difficulty, a great deal difficulty or inability to perform the activity^[10]. Validity and reliability have been established for most of these measures^[20,21].

Target muscles for Btx A injections were selected on the basis of clinical examination: the intramuscular injections were placed into muscles exhibiting an increased muscle tone, using the anatomic landmarks from electromyography.

Solutions of BtxA were prepared by diluting freeze-dried neurotoxin (BOTOX® Allergan Inc., Irvine, CA) with 0.9% preservative-free saline to a concentration of 100 units/ml.

In our study, we followed assessment and treatment protocol, dosing, injection sites, as suggested by The Spasticity Study Group.

We used statistics at a 5% level of significance. Mean and standard deviation of the mean were calculated for descriptive purposes. Efficacy of treatment was assessed using Student's t-test for comparison with the baseline.

Table 3
Demographic profile and details of stroke

Characteristics		
Age (years)		58, 5 ± 4, 7
Sex		
	Male	36
	Female	20
Type of stroke		
	Ischemic	46
	Hemorrhagic	9
Hemiparetic arm		
	Dominant	30
	Non-dominant	26
Duration of stroke (year)		2, 3 ± 0, 7

Table 4
Units of Botulinum Toxin A Injected into Upper Limb Muscles

Clinical pattern	Potential muscles involved	Botox Dose /Units	No. of Injection Sites
Flexed elbow	Brachioradialis	50	2
	Biceps	100	4
	Brachialis	50	2
Pronated forearm	Pronator quadratus	25	1
	Pronator teres	40	1
Flexed wrist	Flexor carpi radialis	50	2
	Flexor carpi ulnaris	40	2
Thumb-in-palm	Flexor pollicis longus	15	1
	Adductor pollicis	10	1
	Opponens	10	1
Clenched fist	Flexor digitorum profundus	15	2
	Flexor digitorum superficialis	50	4

Table 5
Change in Mean Scores for the Efficacy Variables

Measures	Baseline	1 week	4 weeks	12 weeks	16 weeks
MAS	3.72 (1.18)	2.56 (0.83)*	2.35 (0.62)*	2.50 (0.74)*	3.17 (1.37)*
Motricity index: Arm score	37.2 (9.3)	46.3 (5.1)	47.1 (4.8)	45.5 (3.2)	38.1 (4.5)
Limb position at rest					
Elbow	65.7 (12.8)	55.1 (12.3)	52.1 (10.8)	57.2 (15.8)	63.7 (13.8)
Wrist	37.3 (21.6)	25.6 (13.6)	24.8 (10.2)	24.6 (11.2)	29.5 (20.6)
Fingers	1.32	2.25 (0.5)*	2.76 (0.75)*	2.7 (1.02)*	1.5 (1.08)*
Pain score	3.6 (0.8)	2.2 (1.2)*	1.8 (0.8)*	1.7 (0.8)*	2.8 (1.2)
Cleaning the palm of the affected hand	2.35 (0.5)	1.28 (1.06)*	1.02 (0.82)*	1.15 (0.92)*	1.7 (0.95)
Cutting of fingernails of the affected hand	2.13 (0.85)	1.1 (0.63)*	1.0 (0.72)*	1.08 (0.61)*	1.9 (0.83)
Putting the affected arm into the sleeve	2.5 (0.42)	1.3 (0.72)*	1.3 (0.81)*	1.28 (0.54)*	1.95 (0.42)

* = p value < 0.05

RESULTS

Fifty-six patients were enrolled in the study and none withdrew. The demographic profile and details of stroke are shown in table 3. All new patients were having physical treatment three times a week, 15 of them were receiving anti-spasticity medications. The number of injected muscles varied from two to six per limb and the maximum dosage given at a single session was 400 IU. The dose of Botulinum toxin injected into each muscle is given in table 4. Improvements after treatment were seen in most outcome measures, these all being related to changes in the treated muscles.

At baseline, patients demonstrated increased mean muscle tone in the target muscles, which indicated marked to considerable spasticity (Table 5). At follow-up, significant decrease was observed at 1, 4 and 12 weeks after treatment. The best change from baseline was recorded at week four. By week 16, muscle tone reduced to near baseline values. No consistent significant changes in tone were seen in other non-injected muscle groups in the paralyzed upper limb. Although there was improvement of the motor control in the upper limb at 1, 4 and 12 weeks after treatment measured by the arm score, no functional improvement was recorded by BI. Significant change of limb position at rest was observed following treatment with Botox A only at fingers. Pain as a primary spasticity-related complaint was present in 36 of our patients. In 25 (69%) of them, pain was associated with muscle spasms. Our study showed significant relief of pain at 1, 4 and 12 weeks following Btx injections.

Patients' global response to treatment was 1, 95 (± 1, 2), 2, 09 (± 1, 1) and 2, 03 (± 0.8) at 1, 4 and 12 weeks follow-ups respectively. Significant improvement was shown for the three different tasks performed by the patients at two weeks and one, two and three months after treatment. Adverse effects occurred in four patients. three patients had mild pain at injection site and one patient had flu-like symptoms.

DISCUSSION

The present study demonstrated that treatment with Botulinum toxin A reduced muscle tone in patients with post-stroke upper limb spasticity and confirmed the findings of previously reported open label studies^[18,23,24] and controlled trials^[10,16]. Clinically, meaningful and statistically significant improvements in the tone of the flexors muscles as measured by MAS were observed one week after the injections had been administered and these changes were sustained throughout the 12 weeks follow-up period.

Although Btx A resulted in significant reduction of muscle spasticity there was no overall effect on the global disability score (BI). This is hardly surprising because the global assessment scale has a low level of sensitivity. BI includes mobility and continence items that are unlikely to be affected by localized treatment of upper limb muscle spasticity. In similar studies, other investigators did not observe a reasonable improvement on global functional outcome measures, such as Barthel index^[23] and the functional independence measure (FIM)^[9]. This suggests that individualized goal-attainment scales are more relevant outcome measures in studies of this nature^[8,16]. In this study we assessed the improvement in specific areas of functioning, hygiene and dressing by selecting three functional tasks, and we used individualized approach based on the distribution of spasticity in the individual patient that had given a more accurate indication of the effects of treatment in functional disability. Significant improvement was recorded for three functional activities within the three months period following the Btx A injections.

The study showed the definite analgesic effect of Botulinum toxin A. The pathogenic mechanism of spasticity-associated pain has not been fully established yet. One hypothesis is that prolonged and abnormal muscle contractions or tonic activation by descending motor pathways are able to compress the muscles own vasculature and/or to consume large amounts of oxygen, forcing the muscle to perform contractions under ischemic conditions^[25]. Ischemic contractions activate group IV muscle nociceptors or maintain the flexor reflex^[22] most likely by release of bradykinin, prostaglandins (PGE 2) and potassium ions. These inflammatory substances in turn lead to further reflex spasm of the muscle and contribute to the vicious cycle, which is inhibited by the blockage of neuromuscular transmission with intramuscular Btx A injections.

The study has the limitations of any open trial. All improvements were confined to target muscles, and spasticity of untreated regions in the same limb was unchanged from the baseline measurements.

In addition, the treatment was an adjuvant to rather than a replacement for ongoing physical therapy.

In conclusion, Botulinum toxin A has promise as an adjunctive treatment for selected patients with post-stroke spasticity of the upper limb refractory to physical and medical treatments. Benefit usually lasts for three months and side effects are minor and transient, but its role in long-term treatment of spasticity and cost effectiveness will require further study.

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