Intramuscular Injection of Botulinum Toxin for the Treatment of Wrist and Finger Spasticity after Stroke

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SUMMARY

Botulinum toxin is effective in reducing spasticity post stroke. As there are limited data on post stroke spasticity in Asia, we undertake this study to determine the effectiveness and safety of intramuscular injection of botulinum toxin type-A (BTX-A), in the treatment of chronic focal post-stroke hand spasticity, and the impact of BTX-A on the activities of daily living and quality of life, in comparison to placebo, in Malaysian stroke patients. This was a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of BTX-A in 27 subjects with wrist and finger spasticity after a stroke. The outcome measures were assessed with the Modified Ashworth Scale (MAS) to assess spasticity of the flexor muscles, Barthel Index (BI) for activities of daily living and EQ-5D and EQ VAS for quality of life. Assessments were performed at baseline and 1 and 3 months after injection. Compared to placebo, the BTX-A group had greater improvement in the flexor tone of the wrist and fingers ($p=0.001$ and $p<0.001$, respectively), at first month follow-up visit and sustained the improvement through to three months. Although there was an improvement in the measures of global function and quality of life in the BTX-A group, there was no significant improvement in between the two groups. No serious BTX-A related adverse effects were reported. The results of this study demonstrate that intramuscular injection of botulinum toxin A is safe and effective in the treatment of chronic focal post-stroke spasticity of the hand.

KEY WORDS:
Post stroke spasticity, Botulinum toxin A

INTRODUCTION

Stroke is a leading cause of serious long term disability. Despite considerable rehabilitative efforts, the prognosis for recovery of upper limb function after a stroke remains poor. Arm involvement is common with weakness up to 69% at admission to hospital[1]. Long term recovery of arm movement is often poor in patients presenting with a completely paralysed arm. Impairment in the upper limb function contributes to reduced quality of life, increases dependence and interferes with rehabilitation and functional recovery. In patients with complete arm paralysis, spasticity can be an important contributor to disability, by causing pain or interfering with hygiene and dressing.

The conventional treatment for severe upper limb spasticity includes neural depressants (baclofen, benzodiazepines, clonidine, and tizanidine), muscle relaxants (dantrolene sodium) and nerve blocks (phenol, alcohol). These oral agents are limited by their side effects such as generalized weakness and sedation[2] whereas the nerve blocks cause dysesthesia and local tissue necrosis. Injections of botulinum toxin A have revolutionized the treatment of focal spasticity. It is an established treatment for squint, blepharospasm, hemifacial spasm, torticollis, focal dystonias and limb spasticity. Although there are numerous studies evaluating botulinum toxin A in upper limb spasticity from stroke[3-8], the data in the Asian population is still lacking. We performed this study to assess the effectiveness, safety and the impact of botulinum toxin on activities of daily living and quality of life in post stroke hand spasticity in the Malaysian patients.

MATERIALS AND METHODS

This was a randomized double blind placebo controlled study, conducted from June 2006 to November 2006 at Hospital Universiti Kebangsaan Malaysia (HUKM). We included subjects who were at least 21 years of age, had stroke at least a year earlier, had focal spasticity of the wrist and fingers at least three months before enrollment and the muscle tone score of more than or equals to 2 on the Modified Ashworth Scale (MAS). Exclusion criteria were a fixed muscle contracture or profound muscle atrophy in the spastic limb, prior treatment of the limb with botulinum injection or nerve blocks, treatment with agents affecting neuromuscular transmission, neuromuscular diseases, active infection at the injection sites or systemic infection, and pregnant or lactating women. Subjects were randomly assigned to receive a total dose of 80 units of botulinum toxin A (Botox®, Allergen, Irvine, CA, USA) or placebo. 2.2 mls of 0.9% saline (0.2 ml to compensate for dead space) were reconstituted in one vial of Botox containing 100 units. Twenty units (0.4 mls) of Botox or 0.4 mls saline (placebo) were injected in each muscle of wrist flexors (flexor carpi radialis, flexor carpi ulnaris) and finger flexors (flexor digitorum superficialis, flexor digitorum profundus) by a single injector. Following injection, all patients underwent regular physiotherapy sessions, each lasting one hour, twice weekly for three months.

Subjects were assessed at baseline, month 1 and 3 for muscle tone and global measures of function and quality of life. The tone of the wrist and finger flexors was evaluated with the use of the five point Modified Ashworth Scale (MAS)[10]. MAS measures resistance to passive movements according to the

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following scale: 0 implies no increase in muscle tone; 1 implies slight increase in muscle tone with a catch and release, or minimal resistance at the end of the range; 2 implies as 1 but with minimal resistance through the range of movement following catch; 3 implies more marked increase tone through range of movement; 4 implies considerable increase in muscle tone, passive movement is difficult; and 5 implies affected part(s) is rigid in flexion or extension.

The global measure of function was assessed using Barthel Index (BI)[11] of activities of daily living. Barthel Index consists of 10 items that measure a person's daily functioning, specifically the activities of daily living and mobility. The items included feeding, moving from wheelchair to bed and return, grooming, transferring to and from a toilet, bathing, walking on level surface, going up and down stairs, dressing, continence of bowels and bladder. The assessment was used to determine a baseline level of functioning and could be used to monitor improvements in activities of daily living over time. The items were weighted according to a scheme. The person received a score based on whether they had received help while doing the task. The scores for each of the items were summed to create a total score. The higher the score the more "independent" the person. Independence meant that the person needed no assistance at any part of the task. If a person did any of the task about 50% independently then the "middle" score would apply to that particular task.

Subjects were requested to fill in a five-point subjective health-related quality of life questionnaire, EuroQol-5 Dimensions (EQ-5D) with a visual analogue scale (EQ-VAS). The EQ-5D consisted of five simple health-related quality of life questions, measured overall health state (covering mobility, self-care, daily activities, pain or discomfort, anxiety and depression) and the visual analogue score (VAS) measured current health status[12]. The EQ-5D was scored, based on weights, one representing perfect health. VAS captures the self-rating of current health status using a visual "thermometer" with the end points of 100 (best imaginable health state) at the top and zero (worst imaginable health state) at the bottom. Adverse events were assessed at each follow up visit. A serious adverse event was defined as an event that was fatal, life threatening or permanently disabling or that required hospitalization.

The study was approved by the hospital research and ethics committee. Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 12.0. Both t-test and chi-square test were used to analyze, the continuous and categorical data, respectively in the baseline characteristics. Statistical analyses were performed using non-parametric techniques as the data were not normally distributed. A p value < 0.05 was considered significant.

RESULTS

A total of 52 subjects were enrolled in the study of which 27 received botulinum toxin and 25 received placebo. The baseline characteristics of the subjects did not differ significantly between the two groups (Table I).

Subjects treated with botulinum toxin had greater improvement in the principal target of treatment than did subjects who received placebo. In the BTX-A group, there was a significant improvement in the MAS of the wrist flexor ($p=0.001$) and finger flexor ($p< 0.005$) muscles (Table II) compared to placebo. In addition, patients in the BTX-A group had significantly greater improvement in the MAS scores of the wrist flexors at 1 ($p< 0.001$) and three months ($p<0.001$) compared to baseline (Figure 1 and 2). There were no significant improvements in the MAS of the wrist and finger flexors in the placebo group compared to baseline.

Patients in the BTX-A group had significant improvements in the median scores of the BI, EQ-5D and VAS at all follow-up visits compared to baseline (Table III). There were no significant changes in the BI, EQ-5D and VAS between the BTX-A and the placebo groups at all follow-up visits (Table IV). There were no adverse events reported by the two groups.

DISCUSSION

Intramuscular injection of BTX-A is effective in the treatment of chronic focal post-stroke spasticity of the hand. Significant improvement in the MAS was noted in the actively treated group (BTX-A) as early as the first month following injection, indicating a reduction of spasticity. The improvement was sustained till the end of the study. This was in keeping with the duration of action of BTX-A, which is between 3-4 months, but this study was not conducted long enough to the point where the effect of BTX-A was expected to wear off.

This was a double blind placebo controlled trial that was comparable to earlier studies[4,7]. Although the study population was about half of an earlier study[7], the muscles injected were similar. However, Brashear[7] used a higher dose of 50 units of botulinum toxin into each muscle. The dose used in this study was lower at 20 units per muscle. Other studies were mainly open labeled, non controlled [3,5,8,9] with a variable botulinum dose injected into a number of muscles in the upper limb. Most of the studies showed an effect in the MAS scores as early as 1 to 2 weeks with sustained improvement till 12 weeks [3-9]. Similarly, this study showed an improvement in MAS scores in 4 weeks that sustain till 12 weeks.

There were no significant improvements seen in the activities of daily living and quality of life measures when comparing BTX-A with placebo. Apart from Brashear *et al*[7] who showed an improvement in the disability assessment scale and Simpson *et al*[4] who demonstrated an improvement in the global assessment of response to treatment, some other studies did not show a significant gain in functional activity[8,9]. The failure to show functional gain in patients with reduction in spasticity is due to several possible reasons. It is possible that spasticity does not contribute to the limitation of function, but the underlying weakness is the only significant cause of activity limitation. The use of Barthel index may not be sensitive to pick up changes in one or two activities among a battery of tasks unaffected by our intervention. Using selected functional hand tasks may be more relevant outcome measures. Perhaps a larger study population may have yielded a significant finding.

In the BTX –A group, there was an improvement seen in terms of the activities of daily living (BI) and quality of life

Table I: Base-line characteristics of the subjects

Characteristics	PLACEBO (N=25)	BTX-A (N=27)	p value
Mean Age (SD)(years)	61.08 (10.9)	60.48 (11.6)	0.849
Gender-no. (%)			**0.618**
Male	15 (28.8)	18 (34.6)	
Female	10 (19.2)	9 (17.3)	
Race			**0.518**
Malay	7 (13.5)	11 (21.2)	
Chinese	13 (25.0)	13 (25)	
Indian	5 (9.6)	3 (5.8)	
Comorbidity			
Hypertension	22 (42.3)	24 (46.2)	1.000
Diabetis Mellitus	10 (19.2)	16 (30.8)	0.165
Hyperlipidaemia	21 (40.4)	21 (40.4)	0.729
Ischaemic Heart Disease	4 (7.7)	3 (5.8)	0.698
Stroke Type			0.179
Cerebral Infarct	22 (42.3)	27 (51.9)	
Intracerebral Haemorrhage	2 (3.8)	0	
Subarachnoid Haemorrhage	1 (1.9)	0	
Duration of Stroke (SD)(months)	40.36 (44.5)	49.70 (35.5)	0.05
Muscle Tone (MAS)			
Wrist Flexors	2	2	0.237
Finger Flexors	3	3	0.689
Global Measures of Functions (Barthel Index)	90	85	0.459
Health-related Quality of Life (EQ-5D)	0.364	0.205	0.846
EQ VAS	55	60	0.427

Table II: Comparison of MAS scores between BTX-A and placebo groups

Muscle Tone (MAS)	**Median (Q_1 , Q_3)**		
Wrist Flexors	PLACEBO	BTX-A	P value
Month 0	2 (2 , 3)	2 (2 , 3)	0.237
Month 1	2 (2 , 3)	2 (1 , 2)	0.001
Month 3	2 (2 , 3)	2 (1 , 2)	0.001
Finger Flexors			
Month 0 (Baseline)	3 (2 , 4)	3 (3 , 4)	0.689
Month 1	3 (2 , 4)	2 (2 , 3)	<0.005
Month 3	3 (2 , 4)	2 (1 , 2)	<0.005

(Q1,Q3)- interquartile range

Table III: Measures of BI, EQ-5D and EQ VAS in the BTX-A group

	Median (Q1 , Q3)			
	0 month	1 month	3 month	p Value
Global Measures of Functions (BI)	85 (75 , 100)	90 (75 , 100)	85 (75 , 100)	0.041
Health-related Quality of Life (EQ-5D)	0.205 (0.205 , 0.682)	0.364 (0.205 , 0.682)	0.523 (0.205 , 0.682)	0.045
Visual Analog Scale (EQ VAS)	60 (50 , 70)	70 (60 , 80)	70 (55 , 80)	0.042
(Q1,Q3)- interquartile range				

Table IV:Comparison of BI, EQ-5D and EQ VAS between BTX-A and placebo groups

	Median (Q1 , Q3)		
Global Measures of Functions (BI)	PLACEBO	BTX-A	P value
Month 0	90 (42.5 , 95)	85 (75 , 100)	0.459
Month 1	90 (42.5 , 97.5)	90 (75 , 100)	0.382
Month 3	90 (42.5 , 97.5)	85(75 , 100)	0.393
Health-related Quality of Life (EQ-5D)			
Month 0	0.364 (0.046 , 0.682)	0.205 (0.205 , 0.682)	0.846
Month 1	0.364 (0.046 , 0.841)	0.364 (0.205 , 0.682)	0.712
Month 3	0.523 (0.046 , 0.921)	0.523 (0.205 , 0.682)	0.941
Visual Analog Scale (EQ VAS)			
Month 0	55 (40 , 72.5)	60 (50 , 70)	0.427
Month 1	60 (45 , 80)	70 (60 , 80)	0.442
Month 3	60 (45 , 80)	70 (55 , 80)	0.363

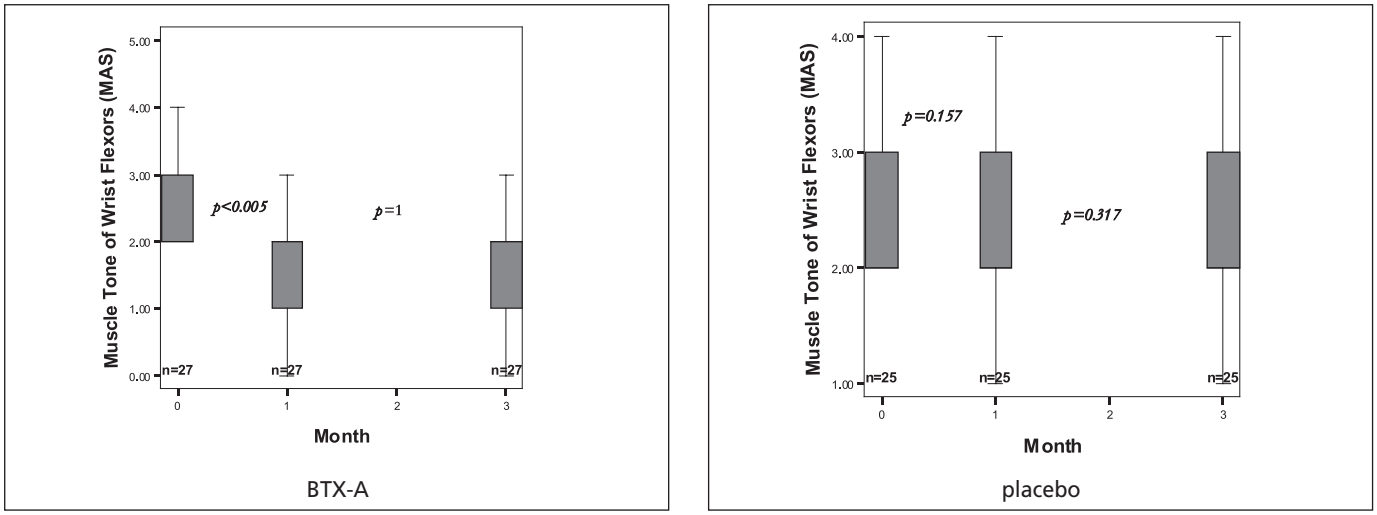

Fig. 1: Boxplot comparing MAS scores of the wrist flexors between BTX-A and placebo groups

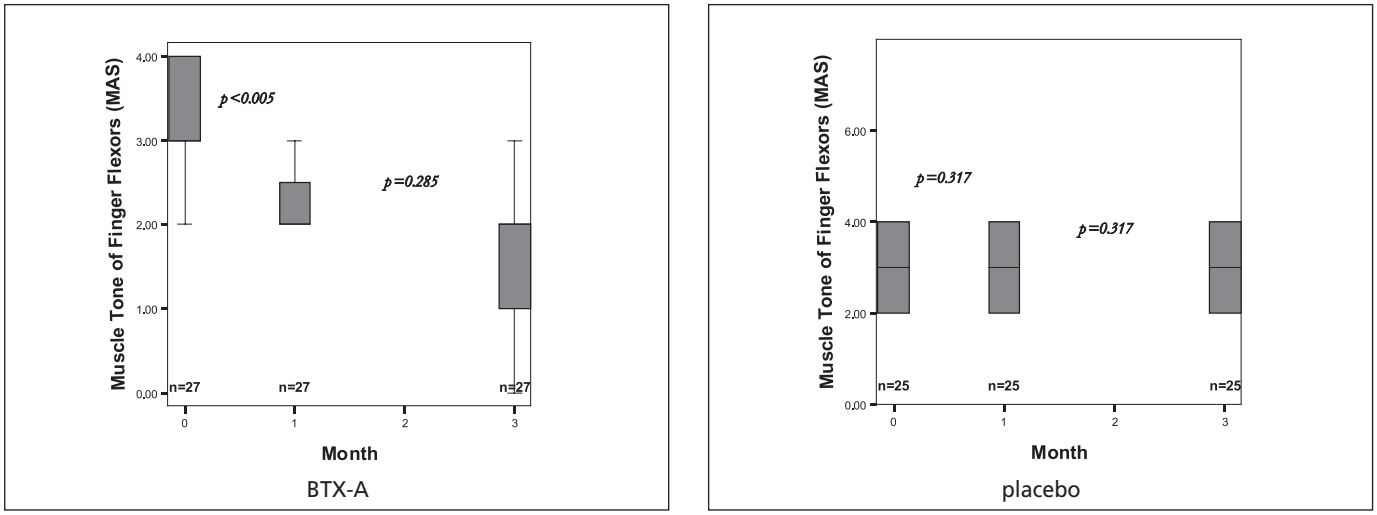

Fig. 2: Boxplot comparing MAS scores of the finger flexors between BTX-A and placebo groups

(EQ-5D and EQ-VAS). An improvement in the upper limb spasticity has a large impact on the global measures of function. Thus, Botulinum toxin dose not only reduce muscle spasticity but also improves the functional disability and quality of life.

Injections of botulinum toxin appear to be safe as there are no reported adverse events. This is consistent with the localized effect of botulinum toxin, which minimizes the risk of systemic adverse events. Our findings conclude that intramuscular injections of botulinum toxin is safe and effective in the treatment of chronic focal post-stroke spasticity of the hand. Improvement in the activities of daily living and quality of life measures are only seen in the BTX-A group.

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