Botulinum toxin A in the treatment of hemiplegic spastic foot drop – clinical and functional outcomes.

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ABSTRACT

Purpose of study: This study investigated the effects of intramuscular Botulinum toxin A (BTX-A) in 7 ambulatory chronic hemiplegic subjects (5 male, 2 female) who had spastic hemiplegic foot drop.

Basic procedures: An open label study involving intramuscular injections of Botulinum toxin A (dilution 10U/0.1ml) was performed in ambulatory chronic hemiplegics. Tone as measured by the Modified Ashworth Scale (MAS), passive ankle joint range of motion (PROM), briskness of ankle reflexes, gait velocity, motor functional status and effects on the use of walking aids were measured at baseline, 3 and 12 weeks post-injection.

Main findings: All subjects except 1 showed a significant decrease in MAS from 3.43 +/- 0.54 at baseline to 2.0 +/- 1.15 at 3 weeks post-injection, which was maintained during the 3 month study duration. The median change in PROM was 17.0 degrees (SD 12.1 degrees) at 3 weeks and 5.0 degrees (SD 7.1 degrees) at 12 weeks (p = 0.25) Gait velocity and Modified Barthel Index mobility scores which measured motor functional status were not significantly altered post-injection. The injections were generally well-tolerated and there were no serious adverse side effects.

Principal Conclusions: Although significant decreases in muscle tone were observed and maintained after intramuscular Botulinum toxin A during the 3 month study period, this regional intervention did not significantly influence functional status, gait velocity and the use of ambulatory aids.

Keywords: Spasticity, Botulinum toxin A, Plantar flexors, Hemiplegia, Foot-drop

Singapore Med J 2000 Vol 41(5):209-213

INTRODUCTION

Spasticity has been widely defined as "a motor disorder characterised by a velocity-dependent increase of muscle tone characterised by exaggerated monosynaptic tendon reflexes and polysynaptic tonic reflexes, and it constitutes part of the upper motor neurone syndrome[1]." Negative phenomena include motor weakness, impaired motor control, particularly of distal muscle groups, fatigue and increased energy expenditure after ambulation. When it affects distal lower limb muscle groups such as the ankle plantarflexors, equinovarus foot position on stance, reduced ambulatory speed, gait dysfunction and increased risk of falls may result. Lower limb spasticity may be a major cause of disability following brain injury.

Conventional treatments for spasticity include passive stretching, physical modalities, splinting and use of orthotics, none of which produce long-lasting results. Medications seldom produce useful reductions in spasticity without producing a significant degree of motor weakness and sedation which may interfere with functional activities[2]. Intrathecal Baclofen pump reduces spasticity but is an invasive and expensive mode of treatment requiring close monitoring of the pump and patient[3]. Regional neurolytic procedures such as motor point blocks with intramuscular phenol or alcohol injections produce selective and more permanent reductions in muscle tone, but may carry with them the risk of painful dysaesthesias and permanent nerve palsy. Neurolytic blockade may be irreversible and requires precise localisation which may be painful. Inadvertent intravascular injection of phenol is potentially dangerous and may lead to seizures, cardiovascular collapse and death.

Intramuscular injections of Botulinum toxin A offer reversible, relatively painless, selective, dose-related weakness of targeted muscles by impairing the release of acetylcholine at the presynaptic neuromuscular junction. These beneficial effects occur without the side effects of sedation, dysaesthesias and seizures[4]. Local injections of Botulinum toxin A have been used successfully in the treatment of focal dystonias such as writer's cramp and idiopathic limb dystonia, and focal adductor spasticity[4]. Recently, it has also been used in the treatment of upper and lower limb spasticity in hemiparetic patients after stroke[5]. However, few studies have

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studied the correlation between reduction in spasticity of the ankle planterflexors and motor functional status[6-8].

This study was designed to study the effects of Botulinum toxin A (BTX-A) on spastic foot drop in chronic hemiparetic patients, with particular regard to whether changes in tone and range of motion at the ankle joint result in changes in motor functional status and walking speed.

METHODS

Subjects

This study used a prospective open-labelled design involving patients with chronic hemiplegic spastic foot drop. No randomisation, observer blinding or placebo treatment was undertaken. All subjects in this study were recruited from both inpatient and outpatient rehabilitation sources locally, between August 1996 - July 1998. Only ambulant subjects with supraspinal spasticity involving the ankle planterflexors of Modified Ashworth grade greater than 2 (maximum score of 4) who were at least 6 months post-event were included in the study[9]. Subjects who had spasticity secondary to spinal cord injuries or fixed joint/soft tissue contractures or significant heterotopic ossification limiting joint range of motion were excluded. All systemic spasmolytic drugs (Baclofen, Dantrolene Sodium, Diazepam) were discontinued for at least 1 month prior to commencement of the study.

Procedures

Both medial and lateral heads of the affected gastrocnemius muscle were injected using motor point localisation by peripheral electrical stimulation. Repetitive monopolar stimulation technique was employed, using a single channel (maximum current of 5mA) Stimuplex nerve stimulator for all patients. Anatomical landmarks for motor point localisation were utilised according to standard electromyographic texts[10]. Botulinum toxin A (BTX-A) (10U/0.1ml dilution with preservative-free normal saline) was injected using a monopolar 22G Teflon-coated needle. Motor point localisation and injection of BTX-A were performed through the same needle.

The average dose of Botulinum toxin A injected was 214.3 +/-37.9 units per limb. The maximum dose of BTX-A used was 300 units per limb. No repeat or booster injections were administered during the study period. The follow-up period was 3 months. Any concomitant physiotherapy, home exercise regimes or pre-existing use of splints were allowed to continue without disruption during the 3-month study period.

This study was sponsored by a research grant from the National Medical Research Council, Singapore.

Assessments

These were performed at baseline, 3 and 12 weeks following initial injection by independent observers (rehabilitation physician and senior physiotherapist). These consisted of measurements of tone, hyper-reflexia, passive ankle joint range of motion (ROM), walking speed and motor function.

The Modified Ashworth Scale (MAS) graded 0-4 was used to objectively assess muscle tone[9].

The presence or absence of hyper-reflexia of the deep tendon reflexes at the ankle joint and passive range of motion of the ankle joint with the knee extended in the supine position was measured using a goniometer.

Time taken to ambulate a fixed distance (21.6 meters) was recorded by a senior physiotherapist using a digital stopwatch. The shortest time taken for 2 consecutive walking trials was recorded. This reading was used to calculate walking speed in metres/second for each subject at each assessment.

Functional status was measured using the mobility subscores of the Modified Barthel Index (MBI) for functional activities of daily living. The total mobility subset score was forty[11]. The need for walking aids and orthoses was also recorded at each assessment. Any adverse side effects were also recorded at follow-up interview by an independent rehabilitation physician. The use of subjective scales using numeric pain intensity ratings and quality of life indices could not be meaningfully interpreted in this study because of the presence of significant aphasia in 3 patients.

Statistical analysis

To facilitate computation of data, categorical variables of the Modified Ashworth Scale were assigned numerical values, designated as “computed MAS scores” in this study. (MAS value 0 = 0, MAS value 1 = 1, MAS value 1+ = 2, MAS value 2 = 3, MAS value 3 = 4, MAS value 4 = 5). Similarly, descriptive variables in the scale used to classify briskness of ankle reflexes and these were assigned numerical values to facilitate computation. (Normal ankle jerks = 1, Hyper-reflexic ankle jerks = 2, Brisk ankle jerks =3).

Basic descriptive statistical analysis using the Statistical Programme for Social Sciences (SPSS) was employed for analysis of all data. Non-parametric tests were used to analyse changes in the various parameters. As the number of subjects was small, the Friedman two-way ANOVA test was used in this study. The level of statistical significance for all tests was set at $p < 0.05$.

RESULTS

Altogether, seven chronic hemiplegic subjects (5 male, 2 female) gave informed consent to participate in this

study. Their mean age was 51 +/- 31 years (range: 39 - 70 years). In all cases, the etiology was a cerebrovascular event (5 thrombotic, 2 haemorrhagic) and the mean interval from stroke to enrolment in the study was 18.1 +/- 10.1 months (range: 8-36 months). All patients were ambulant at the time of enrolment in the study. 4 walked with the aid of an ankle foot orthosis (AFO) and 5 used walking aids (quad canes or single-point canes). 3 patients had severe aphasia (Table I).

All but one had received inpatient rehabilitation treatment at the rehabilitation centre where the study was performed. None were receiving intensive physiotherapy at the time of the study and during the 6-month follow-up period. One patient (number 2) had irregular attendance at an independent outpatient centre, which amounted to less than one hour per week of physiotherapy.

Altogether, 7 hemiplegic limbs with spastic foot-drop were injected (5 right-sided, 2 left-sided. All subjects except 1 experienced reduction in MAS scores observed at 3 weeks post-injection. The median change in the PROM from 0 - 3 weeks and 0 - 12 weeks were 17 degrees (SD 12.1 degrees) and 5 degrees (SD 7.1 degrees) respectively (p = 0.25). 3 out of 7 did not experience any clinically measurable decrease in briskness of their ankle jerks, while the remaining 4 did. The mean reduction in degree of briskness of ankle jerks was 0.58 grades. All subjects demonstrated an increase in walking speed however, this did not approach statistical significance. Changes in MBI were more variable with an increase in scores in 4 subjects, no change in 2 subjects and a decrease in 1 subject.

The average MAS score prior to injection with BTX-A was 3.43 +/- 0.54 and this decreased to 2.0 +/ 1.15 at 3 weeks post-injection. (p = 0.02) The decrease in MAS was sustained throughout the study period of 3 months, although there was a mild increase in MAS from the 3rd week to 3rd month post-injection in 1 subject (number 3). This change in MAS scores was statistically significant (Table II).

The median change in passive ROM from 0 -3 weeks was 17.0 degrees (SD 12.1 degrees, p = 0.25) and this change was not sustained over the subsequent 2 months. All subjects except subject 4 had an increase in passive ROM at the ankle joint. Mean walking speed was generally slow and improved by 0.09m/sec at 3 weeks post-injection in all subjects (p =0.07). This increase was maintained over the 3-month study period (Table III).

Functional changes such as the ability to transfer, ambulate on level ground and climb stairs as documented by MBI scores did not change significantly with time although scores tended to increase during the follow-up period (p = 0.10) (Table III). Similarly, the usage of walking aids or AFOs remained unchanged throughout the duration of the study. No patients could be weaned off their walking aids or AFO's during or after the study period.

Table I. Demographic variables of patients.

Subject	Age (years)	Sex	Diagnosis	Stroke Duration (months)	Walking aid/Brace
1	41	F	L Basal Ganglia Haemorrhage	24	Quad cane/ No AFO
2	42	M	R Intracerebral Haemorrhage	13	Quad cane and AFO
3	41	M	L MCA infarct	23	Quad cane and AFO
4	69	M	L Striatocapsular infarct	36	Single point cane/No AFO
5	56	M	R parieto-occipital infarct	9	Quad cane/ No AFO
6	70	F	L MCA infarct	8	No aid/AFO
7	39	M	L Basal Ganglia infarct	14	No aid/AFO

Legend: M - male, F - female, R - right, L - left, MCA - Middle Cerebral Artery, AFO - Ankle Foot Orthosis

Table II. Computed Modified Ashworth Sale Scores.

Patient	0 weeks	3 weeks	12 weeks
1	3	2	2
2	4	2	2
3	3	1	2
4	3	3	3
5	3	0	0
6	4	3	3
7	4	3	3
Mean (S.D.)	3.43 (0.54)	2.0 (1.15)	2.14 (1.07)

Table III. Changes in tone, ankle jerks, gait velocity and Modified Barthel Index scores.

Mean (SD)	MAS	Ankle jerks (computed values)	Gait Velocity (m/s)	MBI (mobility subset)
0 weeks	2.86 (0.54)	3.0 (0.0)	0.22 (0.09)	26.9 (8.15)
3 weeks	1.50 (1.16)	2.42 (0.54)	0.31 (0.13)	28.6 (8.07)
12 weeks	1.64 (1.07)	2.71 (0.49)	0.31 (0.21)	30.4 (8.44)
Chi-square value	7.79	2.57	5.25	4.57
P value	0.02*	0.27	0.07	0.10
DF	2	2	2	2

Legend: SD - Standard Deviation, MAS - Modified Ashworth Scale, MBI - Modified Barthel Index

** statistically significant*

Compliance with post-injection follow-up was 100%. In general, adverse side effects were minimal, the commonest being transient local pain and swelling at the injection site which did not persist more than 3 days in 2 subjects (28.6%). The remainder did not complain of any side effects. No systemic side effects were reported. 3 out of 4 non-aphasics felt that they had improved subjectively with regards to tone reduction and gait improvements during the study period and the procedure and side effects were well-tolerated.

DISCUSSION

The only parameter which achieved consistent positive gains throughout the 3-month study period was muscle tone as measured by the MAS. Walking speed, changes in ankle joint passive ROM and briskness of ankle jerks did not show significant changes after injection with BTX-A. All subjects except 1 demonstrated a significant reduction in tone observable within 3 weeks of injection after BTX-A. This response rate of 86% was comparable with results of other studies[7]. This reduction in tone was attributed to the neuromuscular blockade effect of the toxin as the mean post-stroke duration of 18 months excluded improvements due to spontaneous recovery. Physical therapy was not likely to have attributed to these reductions in tone as only 1 patient received intermittent physical therapy during the study period.

Although the changes in muscle tone after administration of BTX-A in extensor spasticity of the lower limb are encouraging, our data do not show significant positive results with regards to an increase in ankle joint ROM, reduction in ankle hyper-reflexia and more importantly, function (walking velocity and ability to transfer, walk and climb stairs). It was likely that the use of the MBI which is a global functional scale of independence in mobility and activities of daily living, was insensitive to minor functional changes occurring as a result of a reduction in tone in a single joint. The Fugyl-Meyer scale may be more suited to measurements of subtle changes in lower limb function[12]. Using this scale, Burbaud et al managed to document significant positive change in function following BTX-A in extensor lower limb spasticity[13].

That walking function and reliance on assistive devices and orthoses were not affected by the administration of a focal spasmolytic agent acting on a single joint could be explained by the presence of established gait synergy patterns which often affect the entire lower limb, and other negative effects of spasticity such as poor motor control in other proximal joints and impairment of balance.

The absence of concomitant physical therapy during the duration of effect of BTX-A may have also contributed to the lack of significant change in the walking speed of these patients during the follow-up period. Active stretching exercises, use of modalities such as heat or icing to reduce stretch reflex excitability or serial casts to achieve prolonged musculo-tendinous stretch at the ankle joints may aid gait retraining and possibly affect gait velocity.

Another frequently studied parameter in studies on spasticity is the presence of pain relief[14]. The presence of significant aphasia in 3 patients prevented meaningful analyses of this important functional parameter. The side effect profile of BTX-A was safe and no serious side effects were recorded during the study period.

While the majority of studies on BTX-A in extensor spasticity in the lower limb address chronic hemiparetics, none have targeted patients with spastic hemiplegia in the acute (less than 3 -6 months) post-stroke recovery phase[5 6,7,8,15]. It is possible that modifying tone in this group of patients who are still spontaneously recovering and receiving intensive rehabilitation may yield more promising functional results.

From this modest study, BTX-A injection of the gastrocnemius muscle is effective in reducing plantar flexor spasticity in chronic hemiplegics but does not improve functional outcome or gait velocity. Further research comparing the effectiveness of BTX-A with other inexpensive neurolytic agents such as ethyl alcohol which is extensively used in our centre for spasticity management may help physicians focus health care resources more effectively.

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