A Literature Review on the Efficacy and Safety of Botulinum Toxin: An Injection in Post-Stroke Spasticity

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ABSTRACT

Background: A variety of techniques for the management of spasticity have been suggested, including positioning, cryotherapy, splinting and casting, biofeedback, electrical stimulation, and medical management by pharmacological agents, Botulinum toxin A (BTA) is now the pharmacological treatment of choice in focal spasticity. BTA by blocking acetylcholine release at neuromuscular junctions accounts for its therapeutic action to relieve spasticity.

Methods: A computerized search of Pub Med was carried out to find the latest result about efficacy of BTA in management of post stroke spasticity.

Result: Among 84 articles were found, frothy of them included in this review and divided to lower and upper extremity.

Conclusions: BTA is a treatment choice in reducing tone and managing post stroke spasticity.

Keywords: Botulinum toxin A, spasticity, stroke

Review Article

INTRODUCTION

The high prevalence of stroke is a global problem causing well-known long-term disabilities, one of which is spasticity.[1-3] The incidence of post-stroke spasticity ranges from 17% to 38%, with 4-9% of them suffer from disabling spasticity.[4]

Damage to the pyramidal tract and corticoreticulospinal fibers causes the upper motor neuron syndrome. Spasticity is a common post-stroke feature of the upper motor neuron syndrome.[5] It can have a disabling effect because of pain and reduced mobility of the stroke survivor, which may limit the potential effect of rehabilitation. Quality of life can affected by spasticity and can be highly detrimental to daily functional ability. Spasticity can cause urinary incontinence, limit sexual ability, interfere with walking, sitting, and standing, and could generally reduce one's ability of undertaking activities of daily living. The physical limitations associated with spasticity can raise risk for falls and consequent fractures.[6]A recent study showed that 39% of patients after first stroke are spastic after 12 months.[5]

A variety of techniques for the management of spasticity have been suggested, including positioning, cryotherapy, splinting and casting, biofeedback, electrical stimulation, and medical

management by pharmacological agents.[7] Botulinum toxin A (BTA) is now the pharmacological treatment of choice in focal spasticity.[8]

The aim of this review is gathering data about therapeutic usage of BTA in the management of post stroke spasticity in respect of effect in spasticity and motor functions

BOTULINUM TOXIN MECHANISM OF ACTION IN SPASTICITY

Botulinum toxin is a potent neurotoxin which is produced by the bacterium *Clostridium botulinum.*[9] There are seven Botulinum neurotoxinserotypes (A, B, C1, D, E, F, and G), all of which inhibit acetylcholine release at the neuromuscular junction. BTA and Botulinum toxin E cleave the C terminus of SNAP-25, although BTA has the longest therapeutic effect.[10] There is not any general agreement that the extended action of BTA is due to persistence of catalytic activity or prolonged blocking action by the cleaved SNAP-25. For prolonged periods, cleaved SNAP-25 remains associated with the vesicle-docking protein syntaxin, indicating that it plays a continuous role in blocking vesicle fusion.[11] Nevertheless, this is probably not the only mechanism.[12] The very long duration effect of BTA results in the formation of temporary sprouts which replace for the paralyzed nerve terminal and can cause the wearing-off of clinical effect. A longer period of reinnervation for the parent terminal occurs finally as the sprouts die back.[13]

BTA, by blocking acetylcholine release at neuromuscular junctions, accounts for its therapeutic action to relieve dystonia, spasticity, and related disorders. Also, it has additional therapeutic advantages, not necessarily related to neuromuscular transmission; first, blockade of acetylcholine release at autonomic nerve endings, and second, blockade of transmitter release at peripheral nerve endings which use other mediators.

BTA has effects other than peripheral action, indirect effects may also occur on the spinal cord and brain, which are caused by changes in the normal balance of efferent and afferent signals. Side effects associated with administration of BTA fall into three broad categories: (1) Diffusion of the toxin can lead to unwanted inhibition of transmission at neighboring nerve endings, (2) continued blockade of transmission can cause some effects similar to anatomic denervation, such as muscle atrophy, (3) immunoresistance to BTA is another undesirable side effect[14] [Figure 1].

METHODS

A detailed research was conducted in PubMed database during the time period from 1997 to December 2012 and 13,628 articles were identified concerning Botulinum toxin.

RESULTS

Eighty-four studies were identified for inclusion in this review by search for Botulinum toxin, post-stroke spasticity and finally, 40 articles were included in the review, among them eleven are review articles. The individual studies were categorized into the following subsections: Lower extremity, upper extremity, and both upper and lower extremities.

Tables 1-3 provide a brief annotation for each study.

CONCLUSIONS

As of January 2008, two Botulinum toxin serotypes (A and B) are approved by Food and Drug Administration (FDA) for clinical use in the United States. Botox® is approved for the treatment of strabismus, blepharospasm, cervical dystonia, axillary hyperhidrosis, and glabellar lines; and Myobloc® is approved for cervical dystonia. It is also approved in Europe forfocal adult spasticity.[7]

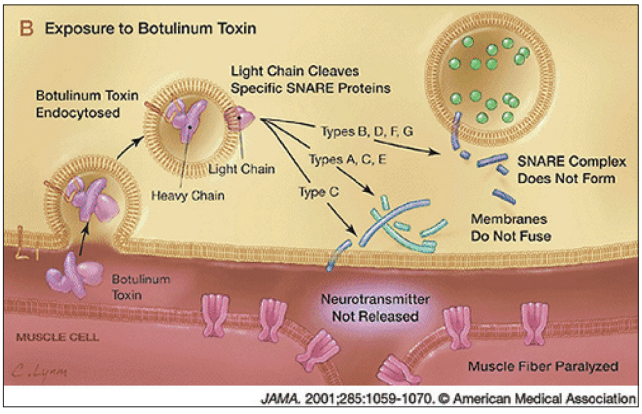

Figure 1: Mechanism of action of botulinum toxin A

Table 1: Lower extremity

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
234	Double-blind randomised placebo-controlled	Equinovarus: Soleus, gastrocnemius and tibialis posterior	500, 1,000 or 1,500 U dysport	Significant reduction in muscle tone, limb pain and dependence on walking aids, No functional improvement	-	2003	Pittock SJ *et al*.[15]
	Review	Equinovarus: Soleus, gastrocnemius and tibialis posterior Toe clawing: Flexor digitorum longus and flexor hallucis longus Great toe permanent extension: Extensor hallucis longus	75-300 U botox or 500-1,500 U dyspor	Effective in all studies	Lack of precise guide to its use, especially its dosage, and its effectiveness compared to that of other treatments	2003	Yelnik AP *et al*.[16]
228	Review	-	-	The use of BTA for lower-limb post-stroke equinovarus caused by spasticity was associated with a small, but statistically significant increase in gait velocity	-	2010	Foley N *et al*.[17]
85	Prospective, multicentre, randomized, double-blind, placebo-controlled	Plantarflexor/ invertor	200 U or 300 U botox	Reduced spasms and improved gait quality, did not alter local spasticity at 12 weeks	-	2012	Dunne JW *et al*.[18]
605	Review	-	-	Pharmacological treatment initiated 6 months post-stroke reduced lower limb spasticity	Period of effectiveness, long-term complications, and a cost-benefit analysis	2012	McIntyre A *et al*.[19]

BTA is a superior treatment for post-stroke spasticity compared to other treatment options like oral therapies, such as diazepam, dantrolene sodium, baclofen, clonidine, gabapentin, and tizanidine; intratechal drug therapies, like intratecha baclofen, morphine sulphate, and fentanyl; focal treatments, such as ethyl alcohol and benzyl alcohol (phenol).[5]

The results of previous studies indicated that BTA is a treatment of choice in reducing tone and

Table 2: Upper extremity

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
20	Prospective clinical trial	Wrist and finger muscles	-	Efficacy of BTA in upper limb spasticity is mainly due to peripheral effects	-	1997	Girlanda P *et al.*[20]
28	Prospective clinical trial	Wrist and finger muscles	-	Repeated BTA injections indicate unchanging effectiveness in the management of focal spasticity after stroke	-	2000	Lagalla G *et al.*[21]
59	Randomized, controlled trial	Wrist and finger muscles	1,000 U dysport	BTA in a dose of 1,000 units reduced muscle tone in patients with post-stroke upper limb spasticity, that sustained for at least 16 weeks	-	2001	Bakheit AM *et al.*[22]
126	Randomized, double-blind, placebo-controlled	Four wrist and finger muscles	200-240 U (20-50 units per muscle) botox	BTA can be useful in improving flexor tone, functional disability, and quality of life in patients with spasticity of the fingers and wrist after stroke	-	2002	Brashear A *et al.*[23]
-	Review	-	100 U botox or (300-500) U dysport	Patients with mild spasticity and a potential for voluntary extensor activity and patients with severe spasticity suffering from problems with positioning and taking care of the affected arm and hand	-	2002	van Kuijk AA *et al.*[24]
-	Review	Pronator teres, flexor carpi radialis, palmaris longus, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis, flexor policis longus	85-300 U botox or 400-1500 U dysport	Improved function in patients with fair distal motricity and low spasticity, and improvement in comfort in those with severe spasticity and low motricity	-	2003	Rousseaux M *et al.*[25]

Contd...

Table 2: Contd...

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
145	Review	BB FCR, FCU FDP, FDS, Brachialis	75-300 U botox or 500-1, 500 U dysport	The use of Botulinum toxin is the only treatment supported by scientific results	Lack of data about the site of injection, how to improve efficacy and influence on neurological recovery	2004	Yelnik AP[26]
18	Prospective clinical trial	Forearm flexor spastic muscles	-	BTA is a valid therapeutic tool in all spastic patients, due to reduction of muscle hypertonia, pain relief, improvement in selected motor performances	-	2004	Miscio G *et al*.[27]
329	Review	-	75-300 U botox or 500-1500 U dysport	BTA decreases spasticity, is a safe therapeutic agent and also, it probably improves the quality of life in upper limb spastic patients	No information about long-term use of BTX-A.	2005	Cardoso E *et al*.[28]
21	Open-label, prospective clinical trial	Wrist and finger muscles	185-300 U botox	BTA injection is an effective, reversible, and safe new treatment option for patients with spasticity. But, functional improvement may be obtained only in certain patients	-	2005	Slawek J *et al*.[29]
27	Randomized, double-blind, placebo-controlled	Wrist and finger flexor muscles	-	Intramuscular injection of BTA is safe and effective in the treatment of chronic focal post-stroke spasticity of the hand	-	2007	Jahangir AW *et al*.[30]
40	Randomized controlled trial	Wrist and finger muscles	1,000 U dysport	BTA has a role in reducing these involuntary arm movements caused by effortful activities	-	2008	Bhakta BB *et al*.[31]
8	Prospective clinical trial	Wrist and finger flexor muscles	-	Some degree of strength and active movement is necessary for the action of BTA on intrafusal fibres	Small size of patient group	2008	Trompetto C *et al*.[32]

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Table 2: Contd...

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
96	Multi-centre, randomized, double-blind, placebo controlled 96	Spastic muscles of the distal upper limb (restricted to muscles acting at elbow, wrist and finger joints)	750-1,000 U dysport	Treatment of upper-limb spasticity with BTA in post-stroke patients, was found to be well tolerated, and efficacious by reducing muscle spasticity and improving the ability to achieve personal functional goals. The benefits were not reflected as a change in quality of life	-	2009	McCrory P *et al*.[33]
16	Prospective observational cohort study	Shoulder girdle or proximal upper limb	Dysport	BTA injection of the proximal upper limb can cause a reduction in spasticity, improvement in passive function and pain	-	2009	Ashford S *et al*.[34]
5	Prospective clinical trial	Upper arm	-	Structures outside the classical motor system, such as the posterior cingulate/ precuneus region, may be associated with the relief of e arm spasticity after stroke	Small size of patient group	2010	Senkárová Z *et al*.[35]
96	Multi-center double-blind, placebo-controlled randomized clinical trial	Injected according to clinical judgement into the dominant spastic muscles of the arm and/or forearm	750-1,000 U dysport	Goal-attainment scaling provides a responsive measure for evaluating focal intervention for upper limb spasticity, identifying outcomes of importance to the individuals, not otherwise identifiable using standardized measures	1. Uncertain injection accuracy and one-third of patients did not receive significant follow-up 2. Goal wording was not always clear 3. Assessment of global benefit is widely used in evaluations of complex intervention	2010	Turner-Stokes L *et al*.[36]

Contd...

Table 2: Contd...

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
145	Prospective, non-randomized, repeated-treatment, open-label study	Wrist and finger muscles	Maximum 400 U per session NT 201 (Xeomin)	Repeated treatments with BTA resulting in significant and sustained improvements in muscle tone and disability	The lack of a comparison group	2010	Kaňovský P *et al*.[37]
109	Multicenter, randomised, double-blind, parallel-group, placebo-controlled study	Flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus and flexor digitorum superficialisflexor pollicis longus, and adductor pollicis	Lower-dose (120-150 U highedose (200-240 U) botox	Higher-dose BTA reduced spasticity in upper limb muscles and improved limb performance in terms of limb position and dressing. BTA is safe and effective in the treatment of post-stroke upper limb spasticity	-	2010	Kaji R *et al*.[38]
21	Double-blind randomized placebo-controlled trial	Wrist and finger muscles	Quarter and half standard dose BTA	Individuals with no arm function may benefit functionally from botulinum toxin within three weeks of stroke	Small size of patient group	2010	Cousins E *et al*.[39]
90	Randomized controlled trial	Wrist and finger muscles	Maximum 1000 U dysport	Muscle selection and BTA dosage were not significantly associated with spasticity severity orwith patient-identified goals, and injector beliefs, rather than patient's characteristics, were the dominant features driving BTA injection strategy	1-Factors other than injectionstrategy may have influenced functional change and goal attainment, 2-small sample size, 3-the degree of multi-disciplinary or client- physician communication at each study site was not reported	2011	Baguley IJ *et al*.[40]
5	Prospective clinical trial	Flexorcarpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, and flexor digitorum profundus muscles	50 U pre-muscle botox	Relief of arm spasticity after stroke may be associated with changes at several hierarchicallevels of the cortical sensorimotor system, including the prefrontal cortex	Small size of patient group	2011	Tomášová Z *et al*.[41]

Contd...

Table 2: Contd...

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
-	Review	-	-	Advantages of early BTA therapy in the acute to sub-acute post-stroke period, while spasticity is still evolving	-	2011	Rosales RL *et al*.[42]
544	Review	Flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), flexor digitorumsuperficialis (FDS), flexor digitorum profundus (FDP), and/or biceps brachii (BB)	Less than 360 U in the upper limb and less than 200 U in the wrist or finger flexor muscles [Onabotulinum toxin A]	Saturating effect of higher muscle tone improvements with increasing BTA doses, and potentially effective BTA doses in selected muscle groups	Dosage limitations of the trials	2011	Yablon SA *et al*.[43]
14	Prospective clinical trial	Wrist and finger muscles	-	Whole brain activation patterns during BTA treatment of post-stroke arm spasticity and further follow up showed predominantly gradual changes within and outside the classical sensorimotor system	-	2012	Veverka T *et al*.[44]
163	Randomized controlled trial	One or more wrist and elbow mover muscles	500 U dysport	Sustained reduction in post-stroke upper-limb spasticity when combined with rehabilitation, Functional use of arms and hands was not affected	-	2012	Rosales RL *et al*.[45]

Table 3: Both upper and lower extremity

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
22	Prospective clinical trial	-	50-100 U [Onabotulinum toxin A]	BTA is safe and effective in treating chronic upper and lower extremities' spasticity. The dosage used is about one-half of recommended doses	-	1998	Viriyavejakul A *et al*.[46]

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Table 3: Contd...

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
204	Review	-	15-600 U botox	BTA injections are safe and effective in the treatment of local spasticity	This study were included traumatic brain, spinal injury and other lesions of the upper motor neuron	1999	Wissel J *et al*.[47]
-	Review	-	-	Lower limb angulations are improved, also, upper limb spasticity, angulation, function, and quality of life were improved	Gait remained difficult to evaluate	2003	Fève A[48]
2187	Data collection from an expert panel experienced	-	-	This study demonstrates that BTA is a cost-effective and clinically efficacious treatment for post-stroke spasticity	Data is derived from a Delphi panel	2005	Ward A *et al*.[49]
20	Open, prospective clinical trial	Using anatomical references	1,500 U per session, 300 U per muscle dysport	If there is no joint motion limitations, the functional gain of post-stroke spastic patient depends on the appropriate dosage, and on the muscle selection, according to the goals established by the rehabilitation team	-	2007	Cardoso E, *et al*.[50]
-464	Review	-	500-1,500 U dysport or 200-360 U botox	BTA improves muscle tone in upper and lower limb spasticity, Improvement was noted by the patients or their caregivers, also it is a safe therapeutic agent	-	2008	Rosales RL *et al*.[51]
782	Review	-	75-300 U botox or 500-1, 500 U dysport	BTA is being increasingly used in patients with	The quality of functional improvement	2009	Elia AE,*et al*.[52]

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Table 3: Contd...

Number of subjects	Study type	Site of injection	Dosage	Conclusions	Limitation	Year	Author
				spasticity as an alternative or add-on to other symptomatic treatments. It is safe and superior to placebo	after BoNT treatment remains a point of uncertainty, which requires to be specifically addressed		
300	Multicenter, double-blind, prospective, randomized	-	Botox	Clinical and cost-effectiveness of BTA standard care vs standard care alone in patients with upper and/ or lower limb post-stroke spasticity	-	2011	Borg J *et al*.[4]
-	Review	-	-	BTA can be an effective treatment in reducing tone and managing post-stroke spasticity. Butits effectiveness in improving function has been controversial	-	2012	Teasell R *et al*.[53]

managing post stroke spasticity. Nevertheless, its efficacy in improving function remains controversial. Also, compared to other pharmacological treatment options noted above, BTA has higher efficacy and less adverse effects.

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