Botulinum Toxin Type A Treatment on Spasticity After Stroke

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Spasticity is a common clinical disease in rehabilitation medication and caused by the damage of motor neurons. The abnormality of muscle tone is caused by stretch reflex action due to increase of relax action and it is stretch dependent [1]. Spasticity could help patients to walk and stand, but it could also disturbed patients to walk, move and nurse. Oral medication treatment is not always satisfactory unless high dosage was used and there might be side effects. The effects of surgical treatment are not long lasting and might bear risks. Although the effect of baclofen treatment have been confirmed, the treatment is not suitable for patients with local spasm, especially for arms. In addition, baclofen could diffuse to the brain and tolerance badly[2]. Physical therapy including motortherapy and physical agent therapy could decrease muscle tone but there is no confirmation for long term effect[3]. Until now, there isn't any effective and safe treatment for spasticity.

Botulinum toxin type A (BTX-A) injection is widely used in treating spasticity caused by different reasons, for example, stroke, brain trauma, spinal damage, cerebral palsy, multiple scleros and amyotrophic lateral sclerosis etc. and showed anti-spasticity effect. In addition, BTXA could selectively reduced the malfunction and symptoms caused by uncomfortable muscle tone which did not affect muscles with beneficial effects on rehabilitation. In January of 2003, the experimental results of upper limb stoke patients using BTXB (MyoBloc) treatment was firstly reported by Brashear. This indicated the usage of a new preparation of BTX on clinical treatment[4]. In this article, the main focus is on the application and discussion of BTXA treatment on spasticity after stroke.

1. Characteristic of Spasticity of Stroke Patient

Spasticity could affect about 65% of stroke patients and symptoms appeared from several days to several weeks after stroke. The symptoms showed by the increase in muscle tone on upper limb flexor (the adductor of shoulder and the flexion of elbow, wrist and arm) and lower limb extensor (stretch of hip, knee and flexion of ankle), and this always along with reflex action, spasm, common contraction of congenerous muscles-antagonistic muscle, pathology, asthenia and tiredness[5,6].

Spasticity could affect the local muscle tension abnormality of minority muscles and

it could also be affect a multi-group of muscles. In most cases, stroke patients showed local muscle spasm as the common symptom. Spasticity could help patients to walk, transfer, back flow of blood in vein and reduced edema etc. However, it could also cause adverse effects by affecting the ADL level, hygiene, shoulder joint and sleep of patients and hence affect the flexion of joints and pressure ulcer. These caused disruption of the neuron muscles recovery. Scholars believe that spasticity have an interference window period. If the treatment was done earlier, the recovery of motor ability of patients would be better[5].

Abnormal position of lower limbs, hip, knee and ankle joint would lead to difficulties of patients to seat on wheel chair. The serious talipes equines resulted difficulties in wearing shoes and using the pedals of wheelchair. In early stage, physical practice could increase the recovery of body function, reduction of blockage of vein and reduction of the loss of lung and heart function which caused by inadequate sports. Spasticity disturbed patients from walk and stand. Kramers de Quervian has reported that spasticity could affect patients' gait and walking ability, the reduction of moment force of hemi-paralysis could lead to the time extension of walking gait[7]. The spasticity of quadriceps muscle of thigh means the flexion of knee joint which affects the contact of foot to the ground. This leads to trail of toes, dash of affected limbs and swing of pelvic girdle.

For the upper limbs, spasms caused by the deformation of hands and arms resulted the loss of voluntary action. These severely affected the ability of patients, for example, eating, bathing, hygiene handling, self-image, balancing and walking ability, even hand and shoulder symptoms in severe cases. In some reports, shoulder pain was showed in 70 to 84% of stroke hemi-paralysis patients and 85% of these patients showed in the spasm recovery period[8]. It might be caused by the position and stereotypy of motion. These damaged the separation of joints and extended the time for recovery[9].

2. Clinical Pharmacology of Botulinum Toxin

Botulism has been discovered for several centuries. *Clostridium botulinum* is one of the Gram negative anaerobic bacteria which could produce 7 types of toxins (A-G)[3]. In the 20s of the last century, BTX-A was firstly purified. The first purification of BTX-A crystalline was success in 1946. The signal transmission of neuron synapse was blocked and this leads to the chemical loss of neuron functions and resulted local muscle paralysis. This technique has been developed to clinical treatment of motor neurological diseases. In 1973, Scott firstly discovered the use of BTXA on

blepharospasm treatment using primates as animal model[10]. In 1980, Scott firstly discovered using BTXA on blepharospasm treatment in human[11]. In the early 80s, Due to the effectiveness of BTXA, it was used in clinical treatment on blepharospasm instead of surgery. After that, BTX-A was also used in treatment of eye muscle dystonia and facial spasm. In 1989, Das and Park firstly published an experimental report of BTXA treatment on spasticity[12]. In 1992, Hesse *et al* published the result of BTXA treatment on spasticity after stoke[12]. After that, more and more clinical researcher use BTX-A treatment on spasticity after stroke to relief the symptoms and to recover the motor function.

Botulinum toxin is classified into 7 types and it could be combined with the nerve of muscles. Among the 7 types, BTXA shows the most powerful effect. In normal condition, acetylcholine(Ach) is release to the synapse by neuro-potential. Ach and sarolemma (prosynaptic membrane) combined with the receptors and this lead to the depolarization of muscles and hence muscle contraction. The combined BTX-A and presynaptic membrane could be separated into light and heavy subunits, and the N terminal could be improved by the light subunit passing through serous membrane to serum. The light subunit and synaptosomal associated protein 25 (SNAP-25) interfere the calcium ions. This leads to the release of Ach from presynaptic membrane and prevent muscle depolarization [14-15].

Different types of botulinum toxin interferes different fusion proteins on neuromusclar junctions. The mechanism of BTX-E is the same as BTX-A and the mechanisms of BTX-B, BTX-D, BTX-F and BTX-G are by the decomposition of the vesicular-associated membrane protein (VAMP). The action of BTX-C is by the decomposition of both Syntaxin and SNAP-25[16]. BTX-B could be used in patients have BTX-A antibody or patient without any effect on BTXA. The mechanisms of BTX-C and BTX-A are the same, BTX-F could be used in patients with BTX-A antibody. Since the duration of BTX-A is shorter (only 5 weeks), clinical application is limited[16].

Two different types of BTX-A products were using outside Mainland China: Botox (manufactured by U.S.A) and Dysport (manufactured by U.K.). 1 unit of Botox is equivalent to 0.4ng BTX-A and 1 unit of Dysport is equivalent to 0.025ng BTX-A. In general, 1 unit of Botox is equivalent to 3-4 units of Dysport[17].

The main local side effect of BTX-A is paralysis. The side effects were mild and appear in a short period of time. The side effects were caused by the distribution of

toxin to other muscles and it could be weakened by time pass. The side effects for the whole body, for example, short period influenza, allergy and asthenia is rare[16]. Muscles resistance to BTX-A could be occurred after multiple injections, but the probability is low. This might be due to the production of BTX-A antibody by patients[18]. There should be at least 12 weeks interval apart from each injection and the dosage for every injection should be control. The resistance problem could be prevented by the above points[3].

3. Clinical Use of BTX-A on Spasticity of Stroke Patients

3.1 Effect of BTX-A Treatment on Spasticity of Upper Limbs

In the recent 10 years, there were many reports related to the spasticity of upper limbs of stroke patients. Studies in early stages were open-ended and the sample size was small. In recent years, there were more and more experiments with random samples and control. Most of these studies demonstrated reduction of spasticity after BTX-A treatment. However, no significant difference was showed between control and treatment groups. There were few experiments with large samples showed significant improvement after BTX-A treatment.

According to Hesse *et al*, muscle spasm could be greatly reduced by local muscle injection of 1600U Dysport under EMG guidance. The personal hygiene of patients has been improved while the score for their moving abilities did not show any change. According to Bhakta *et al*, BTX-A could reduce serious dystonia and improved moving ability effectively and safely. Sampaio *et al*[20] have confirmed BTXA could be used for the treatment on spasticity. However, they also discovered that there is little difference on the ability scoring before and after treatment in most patients. These might be due to treatments were done on hands and fingers extensors but not on elbow flexor. According to Sampaio *et al*[21], 39 cases of severe upper limb spasticity after stroke (for at least 9 months) have underwent multi-centre, random, double blinded and placebo control experiments by using different dosages of Botox (75, 150 and 300U) and placebo. After the injection of BTX-A, significant reduction of dystonia and durable were observed for 6 weeks. However, no significant difference was showed between the treatment and control groups on moving ability, pain management, reliability of patients and the ability on common daily life. These results were quite different between the open-ended experiment done by Bhakta *et al* [19] as well as Pierson *et al* [22]. Bhakta *et al* and Pierson *et al* reported that there as an increased of joints moving area, better management of personal hygiene and improvement of motor ability after BTX-A treatment. Again, no significant improvement was showed in the report by Sampaio *et al*[21]. It might be due to the

higher basic ability of selected patients which resulted smaller improving range. In addition, it might be due to insensitiveness of the scoring method (FIM and Fugel-Meyer).

According to Girlanda *et al*[30] , significant reduction of dystonia and improvement on moving ability were observed among 20 cases of upper limbs spasticity for more than one year. There was significant reduction on M wave and H reflection wave by electrophysiology without any change on H_{max} / M_{max} ratio. These explained that BTX-A have no effect on the excitability of central motor neuron and the reduction of M wave and H reflection wave might due to BTX-A.

According to Bhakta *et al*[24], 82 cases of stroke patients were treated by Dysport (500, 1000 and 1500U) and placebo in parallel experiment. The injection sites included elbow, wrist and finger flexor. Obvious higher score was showed after BTX-A treatment than placebo on modified Ashworth score and the optimal dosage was 1000U. Paralysis was showed in patients using 1500U and the side effects were dosage dependent. There were 40 cases of spasticity after stroke (average 2.7 years) patients were treated by Dysport (1000U) and placebo [25]. 6 weeks after injection, the Ashworth score, dependence and nursing ability of patients has been increased significantly. The improvement for 12 weeks after injection was also showed but the level of improvement is slightly decreased. Similar treatment methods was also used by Smith *et al*[26]. According to Bakheit *et al*, obvious improvement on Ashworth scoring on fingers and wrist flexor was observed in 24 cases with some modifications on injection dosage and injection sites. Although improvements were showed in elbow flexor, there is not any significant difference between the treatment and placebo groups. According to Bakheit *et al*[27], 59 cases were undergo parallel experiment with 1000U Dysport injection. For injection after 4 weeks, obvious improvements were observed when comparing Ashworth score and ROM of limb joints between placebo and treatment groups. For injection after 16 weeks, better results were showed in all patients with Dysport treatment than placebo treatment. According to Wang *et al*[28], 16 stroke patients were treated by BTXA injection with an average dosage of 140U (80-200U). The results showed improvements on dystonia, ROM, griping strength on muscle pain after injection and the duration lasted for 8 to 12 weeks. However, no significant effects were showed on ability score between treatment and placebo groups. The above experiment was an open-ended experiment without any control. According to Rousseaux *et al*[29] , 200-300U BTX-A was injected to the adductor of upper limbs and obvious reduction of spasticity on flexor of forearm, musculus pronator and wrist flexor were showed. The myodynamic of wrist flexor have been

increased while improvements in grasping and releasing object as well as increase of ADL were observed. However, no significant improvements were showed in Nine-hole Peg Test (NHPT). There was a multi-centre, double-blinded and with random control experiment with the largest sample (126 cases) was done by Brashear *et al*[30]. The experiment results showed the reduction of spasticity after treatment while obviously improvements were found on 62% patients' personal hygiene management, pain management as well as their position. The score of treatment group was significantly higher than control group by 27%.

3.2 Effect of BTX-A Treatment on Spasticity of Lower Limbs

There was much less reports of BTX-A treatment on spasticity of lower limbs when comparing BTX-A treatment on spasticity of upper limbs. The efficacy and safety of BTX-A was confirmed in the report of Hesse *et al*[31] and Burbaud *et al*[32]. Obvious improvements were showed including Ashworth score and gait analysis index. According to Burnaud *et al*[32], 23 cases (3.5 months to 10 years after stroke) were investigated by an alternative application of 1000U Dysport and placebo after 90 days. Obvious improvements on gait and less independence were observed after BTX-A treatment on spasticity of upper limbs. However, no obvious improvements were observed on Fugel-Meyer score and walking speed. The longer time the spasticity, the responses to BTX-A were worse. A comparison between lower dose (100U) and normal dose (190-320U) of BTX-A injection to ankle support of 180 cases of talipes equinovarus after stroke was done by Reiter *et al*[33]. The Ashworth score of both groups have been reduced for one score, but the duration period was lesser in low dose treatment. In addition, same level of increment of walking speed and gait were observed for both groups. The associate reactions of upper limbs and the safety of walking were investigated by BTX-A treatment on bicept by Bkaheit *et al*[34]. 8 patients showed obvious relief after 500U Dysport injection. Although improvements on walking were observed among 7 cases, physicians did not discover any improvements on balancing or walking ability.

3.3 Combination of BTX-A and Other Treatment Method

There was not many reports discuss the combination treatment of BTX-A with other methods. A comparison between lower dose (100U) and normal dose (190-320U) of BTX-A injection to ankle support was done by Reiter *et al*[33]. The results between two groups showed similar effects, but the inactive dorsiflexion area of ankle joint of low dose BTX-A injection to ankle support group is lesser than the normal group. According to Hesse *et al*[35], 24 cases of spasticity of upper limbs after stroke were treated by: BTX-A injection (1000U) with electrical stimulation, BTX-A injection

alone, injection of placebo with electrical stimulation and placebo injection alone. The most obvious effect on the reduction of dystonia and improvement on moving ability were showed among the BTX-A injection with electrical stimulation group. The results showed that the treatment results of BTX-A could be increased by local electric stimulation. According to Page, one case with spasticity of upper limbs after cerebral artery infarction for 14 month was treated with combination treatment and modified constraint-induced therapy. The results suggested that the treatment effects could be increased by the combination of other treatment methods.

In conclusion, BTX-A local injection was an effective and safe treatment method. However, further investigations are necessary for some problems such as the timing of using BTX-A, scoring method of clinical effect on specific treatment (especially on moving ability), and the relationship between BTX-A treatment and other treatment methods, etc.

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