Clinical Study of Botulinum Toxin Type A in The Treatment of Dystonia Diseases

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Objective: To study the efficacy of botulinum toxin type A injection in the treatment of dystonia diseases.
Method: 527 patients with dystonia diseases, including 368 patients with hemifacial spasm, 65 patients with blepharospasm, 39 patients with Meige's syndrome, 45 patients with cervical dystonia and 10 patients with other kinds of dystonia diseases, were evaluated on the therapeutic efficacy of multifocal muscles injections.
Result: About the hemifacial spasm and blepharospasm, 154 patients were completely relieved, 233 were remarkably relieved, 39 were partly relieved and 7 had no improvement. About 39 patients of Meige's syndrome, 27 were remarkably relieved, 9 were partly relieved and 3 had no improvement. The improvement also happened after injection in 2~10 days, and it lasted from 10~20 weeks. The local side effects were transient and mild, no systemic adverse and allergic reactions were noted. It was efficient for injection repeatedly.
Conclusion: Botulinum toxin type A local injection is a safe, effective, simple and easy methods for the treatment of dystonia diseases.
Key words: Botulinum toxin; Dystonia diseases; Hemifacial spasm; Blepharospasm; Meige's syndrome; Cervical dystonia

Dr. Scott in the US firstly used Botulinum toxin type A in the treatment of strabismus in 1979 and a successful result was shown. This treatment method gets an increasing concern among neurology professions. It then becomes a common method in treating dystonia diseases and facial spasm. Recently, it has been found to be successful in treating local autonomic nervous function disorder such as hyperhidrosis. We carried out the treatment of autonomic nervous diseases upon the injection of Botulinum toxin type A for 10 years and got a remarkable result. The result is shown as below.

Information and Method

1. Clinical Information

There were 527 patients in total. 368 patients with hemifacial spasm with 199 cases in left side and 169 cases in right side, 65 patients with blepharospasm, 39 patients with Meige's syndrome, 45 patients with cervical dystonia and 10 patients with other

dystonia diseases. 197 patients were men and 333 were women. They were in the age from 15 to 87. All were not be treatable by the method of medicine, acupuncture, physiotherapy, local blockade and surgery. By the diagnosis of CT, MRI and EEG, one case showed left basal ganglia infarction. One showed mild encephalatrophy. One showed cervical vertebrae flexion deformity. One showed Cruveilhier's joint subluxation. No patients showed changes in nervous system, fever, chronic infection diseases and organic diseases.

2. Method

Botulinum toxin type A was developed by the Lanzhou Institute of Biological Products. It is a freeze-dried water soluble crystalline toxin. In the early stage, it was classified into three types, namely 40u, 65u and 100u per ampoule. In 2002, two packages of 50 units and 100 units per vial were available. They should be stored at -20 to -5 ˚C. 2.5u of botulinum toxin type A should be diluted with 0.05ml of 0.9% sterilized normal saline before use. Multifocal muscle injection is performed by 1 ml skin test injector with syringe needle of no. 4.5. Injection site and dosage were determined by the size and the amount of the muscle and the severity of spasm. There were totally 5 injection sites for the treatment of unilateral blepharospasm. They were at the subcutaneous part with the distance of 2-3 mm to the palpebral margin and 5 mm away from the subcutaneous muculus orbicularis oculi. For the patients with bilateral blepharospasm, five more sites on the two sides were required for the injection. For patients with facial spasm, additional injection was required at the site of greater and lesser zygomatic muscle, buccinator muscle, lip, musculus orbicularis oris etc. There were in total 10-12 sites and the typical dosage was 2.5u per site. For patients with cervical dystonia and other dystonia diseases, the dosage is 2.5~15u per site. For the patients with remaining spasm, repeated injection was performed within one week. Each dosage was less than 300u. The overall dosage was less than 400u within one month.

3. Clinical Standard and Evaluation

Hemifacial spasm and blepharospasm were graded according to the severity of spasm. Grade 0 indicated no spasm. Grade 1 indicated the increase of winking caused by external stimuli. Grade 2 indicated a mild spasm with a slight tremor of eyelid muscle and no function barrier. Grade 3 indicated a moderate and apparent spasm with a slight function barrier. Grade 4 indicated a serious spasm and a function barrier such as difficulty in walking and incapability of walking. Complete relief was said if the patients moved from Grade 2-4 to Grade 0 after therapy. Patients from Grade 2-4 to Grade 1-2 and from Grade 4 to Grade 3 were said to be remarkably relieved and

partly relieved respectively.

Dystonia was marked by the Tsui method.

A. Degree of head skewness (0-9 mark)

Twisting (0 mark = none, 1 mark =<15°, 2 marks = 15° - 30°, 3 marks =>30°),

Skewing (0 mark = none, 1 mark =<15°, 2 marks = 15° - 30°, 3 marks =>30°) and

Front-to-back flexion (0 mark = none, 1 mark = mild, 2 mark = moderate, 3 mark = serious)

A is the sum of the above 3 terms,

B is the period of head skewing (0-2 marks), 1 mark = transient, 2 marks = successive and

C is elevation of shoulder (0-3 marks), where

1 mark = slight and transient, 2 marks = slight and successive or serious and transient, and 3 marks = serious and transient.

D is head tremor or convulsion (0-4 marks) where D = Degree X Period.

In Degree, 1 mark = slight and 2 marks = serious.

In Period, 1 mark = transient and 2 marks = successive.

Total = A X B + C + D

Result

About the hemifacial spasm and blepharospasm, 154 patients were completely relieved (35.6%), 233 were remarkably relieved (53.8%), 39 were partly relieved (9.0%) and 7 had no improvement (1.6%). Dystonia showed 5-16 marks before injection and it decreased to 2-10 marks after injection, indicating the improvement after therapy. For the patients with Meige's syndrome, 27 were remarkably relieved, 9 were partly relieved and 3 had no improvement. The improvement was also found in patients of cervical dystonia and other kinds of dystonia diseases. 98.1% of patients showed improvement after injection in 2-10 days and it lasted from 10-20 weeks. The injection dosage could be adjusted according to the therapeutic effectiveness and the side effects. The number of repeated dosage was 30 times. Local side effects found were mild and temporary. It occurred as local edema and ecchymosis at the eyelind and around the mouth. Local side effects were relieved within 2 to 5 days. 234 patients with facial spasm and blepharospasm showed weakness in unilateral eye muscle or partly ptosis. 2 patients with Meige's syndrome were found to have a mild difficulty in swallowing and this could be relieved within a few weeks. No systemic adverse and allergic reactions were noted.

Discussion

Dystonia disease is a common motion disorder disease. It is found that the effect of orally medical treatment is temporary and mild. However, increased medicine dosage

results in systemic adverse and allergic reactions. The treatment of nerve blocking and surgery can cause nervous damage and recurrence of diseases. With the significant effect, few adverse allergic reactions and a simple operation method, Botulinum toxin type A is commonly used in the treatment of neurological diseases such as dystonia diseases.

Bontulinum toxin is an exotoxin produced during the cultivation of Clostridium botulinum. There are totally seven toxins types, namely type A, B, C, D, E, F and G. They are antigenically distinct from each other. The molecular weight of botulinum toxin type A is 150KD. The botulinum toxin molecule is composed of a heavy chain and a light chain connected with a disulfide bridge. The hydroxyl group of the heavy chain binds to the presynaptic membrane of the cholinergic nerve. Translocation of the light chain occurs inside the cell. Release of acetylcholine is inhibited through enzymatic reaction. This results in muscle relaxation.

A small dose of injection into specific muscle end-plate can cause a significant effect of paralysis. [1, 2, 3] From the studies, more than 70% of patients got a sustained improvement for about 3 months. It became effective after repeated dosage. [2] For the last 10 years, the effective rate reached 98% among the 527 patients with dystonia diseases. Since sprouting of new axon terminals results in reestablishment of neuromuscular transmission, repeated dosage is required for every 4-5 months. With the inability of entering blood-brain barrier, it worked only on the terminal of the peripheral cholinergic nerve. It showed no systemic adverse and allergic reactions after repeated injections. According to the studies of the US professions, the therapeutic quantity of the botulinum toxin is only 0.3% and 0.005% of inhaled fatal dosage and oral fatal dosage respectively. It is generally believed that human are highly tolerant of therapeutic bontulinum toxin and it is safe to undergo the treatment. [4]

Blepharoptosis is a common complication of botulinum toxin treatment in facial spasm and blepharospasm. Using botulinum toxin type A for the treatment of dystonia diseases may cause difficulty in swallowing which is mainly caused by local diffusion of the toxin. [5,6] From the observation, only 2 patients with Meige's syndrome had a difficulty in swallowing which no patients with cervical dystonia had any complications. They were the results of injection in the site of unilateral sternocleidomastoid and could be relieved later. In a study of about 7,000 patients with the treatment of botulinum toxin type A, antibodies developed in 12 cases. This showed that the long term repeated injection might cause the development of corresponding antibodies in patients. To minimize the quantity of antibodies, repeated

injection should not be performed within 3 months. In our clinical study, the least interval of every injection was 12 weeks. No development of antibodies was found during the study. Products of botulinum toxin type B which act as the supplements of botulinum toxin type A have been sold in the markets in other countries [4].

To obtain an excellent therapeutic result, it is important to have a precise diagnosis, an accurate allocation and an appropriate dosage. Abundant anatomical knowledge is of great importance as well. It is useful to use electromyogram and in-line electrode needle for the injection if patients have a variety of symptoms. It was found that the typical dosage of 2.5u per site is effective in relieving blepharospasm but not in facial spasm. This was mainly due to the smaller area in muculus orbicularis oculi and buccinator muscle and larger area in musculus orbicularis oris. Supplementary injection after one week was effective in the treatment of the remaining spasm. The number of injection sites can be increased for patients with serious spasms. The asymmetry of the face can be minimized by the method of symmetrical half dosage injection for patients having a higher requirement in beauty.

Since antibodies such as aminoglycoside enhance the effect of botulinum toxin, it is advised that patients taking these medicines should not be treated by the toxin. It should also not be used in patients with motor neuron diseases, myasthenia gravis and Lambert-Eaton's syndrome. It is better not to apply the treatment of toxin in pregnant and breast-feeding women. Botulinum toxin type A local injection is a safe, effective, simple and easy methods for the treatment of dystonia diseases. It can relieve and remove the symptoms of muscle spasm. It will soon be widely used in different applications of treatment as further studies are undergone.

References

1. Schartz FJ, Johnson EA. Properties and use of botulinum toxin and other microbial neutroxin in medicine. *Review Mar*, 1992; 56:80.
2. Hallett M. Chemistry and mode of action of botulinum toxin (abstract). *Muscle Nerve*, 1994; Supple 1:s42.
3. Davia LE. Botulinum toxin from poison to medicine. *West J Med*, 1993; 158:25.
4. Tang XF, Wang YC. Botulinum Toxin Clinical Therapeutic Handbook. 1st ed. People's Medical Publishing House; 2005.
5. Elston JS. Botulinum toxin treatment of hemifacial spasm. *J Neurol Neurosurg Psychiatry*, 1988; 49:827.
6. Jankovic J, Scharts K. Botulinum toxin injections for cervical dystonic. *Neutrology*, 1990; 40:277.