Botulinum Toxin Type A Treatment in Focal Dystonia

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Abstract

Local injection of Botulinum Toxin Type A (LANTOX) in treatment of 15 cases of blepharospasm, 22 cases of lateral facial spasm, 2 cases of Meige's Syndrome, 2 cases of spasmodic torticollis, totally 41 cases, all effective. Basically no systemic reaction occur, local side effects are slight and temporary, duration of medicines is 5 – 28 weeks, mostly 12 – 16 weeks. Can do the supplementary injection, can do replicated injection, no allergic reaction. Clinical observation indicated that LANTOX treatment in focal dystonia is safe, highly effective and easy to operate.

Key words: Botulinum Toxin Type A; Focal dystonia

Primary focal dystonia includes blepharospasm disorder, spasmodic torticollis, lateral facial spasm, laryngospasm, etc. It is a kind of chronic progressive nerve muscle extrapyramidal disease, the therapeutic effects are mostly not ideal. In 1980, Scott from U.S. used botulinum toxin type A (BTXA) in treatment of strabismus. In 1993, Dai from China used LANTOX in treatment of blepharospasm and facial spasm, the efficacy was 92.2%, improvement rate was 7.8%, all treatment are effective. Our department started several therapies from April 1995, the therapeutic effects were good. The results are reported as follows.

Subject and Method

1. Subject

There were 15 cases of blepharospasm, 22 cases of lateral facial muscle spasm, 2 cases of Meige's Syndrome, 2 cases of spasmodic torticollis, totally 41 cases. 27 male cases, 14 female cases. The age ranged from 34 – 76 years, with an average of 55.4 years. The medical state varied from 1 – 20 years. CT examination for 15 cases before treatment, all were normal. The patients tried drugs like carbamazepine, haloperidol, etc, and operation, acupuncture and moxibustion, all ineffective.

2. Method

Grading Before and After Treatment: Classified into 5 grades according to strength of spasm. Grade 0: no spasm; Grade 1: winking action increase upon external stimulations; Grade 2 (light): eyelids and facial muscle slightly jitter, but no

dysfunction; Grade 3 (medium): obvious spasm, with slight dysfunction; Grade 4 (severe): severe spasm and dysfunction, affect living, study and work.

Dosage and Usage: The LANTOX produced by Lanzhou Institute of Biological Products is used. It was diluted to 25U/ml before used. Each pointed was injected 2.5U (equivalent to 0.1mL). Location points of severe spasmodic muscle were selected. i) Blepharospasm: injected into bilateral orbicular muscle of eye, 5 points at internal and external sides of upper and lower eyelids and subcutaneous part of outer canthus temporal. The first total dosage did not exceed 50U, generally used 25U; ii) lateral eyelid facial muscle spasm: injected into orbicular muscle of eye, middle face and musculus orbicularis oris, the first total dosage was 22.5U, not exceed 50U; iii) spasmodic torticollis: injected into bilateral neck muscle: splenius muscle of head, semispinal muscle of head, trapezius muscle, sternocleidomastoid. Over 2 points were selected for each piece of muscle, first dosage was 70 – 110U; iv) Meige's Syndrome: selected 18 points of eyes, face and mouth, total dosage was 55U.

Result

There were 41 cases, all effective after treatment, the efficacy was 100%. The earliest appearance of effect was 6 hours after injection, the degree of spasm decreased, episode decreased, some patients' symptoms completely disappeared after 24 hours of injection. In a case of a 2-year bilateral blepharospasm patient, the grading of spasm decreased from Grade 4 to Grade 0 in the morning after treatment. The shortest duration of drugs was 7 weeks, the longest was 28 weeks, generally 12 – 16 weeks. The curative effects were related to the following factors: i) Patients who have severe spasm and long states of illness processed slower remission in symptoms, and the spasm could not completely disappear, for example, facial spasms patients of Grade 4 seemed to process jitter of mouth angle and facial muscle; ii) for the patients with severe spasm and long states of illness, supplementary injection was probably needed after 1 – 2 weeks of injection; iii) for the patients who were older, the remission of symptoms was a little bit slow; vi) duration of effects in patients of bilateral blepharospasm was shorter than that of lateral patients; v) patients of spasmodic torticollis still needed to take Artane or Valium, but the dosage was obviously reduced; vi) the duration of effects was related to total dosage of drug. For example, the total injection dosage of lateral blepharospasm patients was lower than 17.5U and that of grade 3 blepharospasm patients was lower than 20U. The curative effects were not obvious. After supplementary injection, the symptoms disappeared quickly and the duration increased. Side effects: i) among most of lateral eye and face muscle spasm patients, eye dysraphism 2 – 3 mm occurred or

unable to close eyes; winking movement reduction and mouth angle drop processed in one case; dysphagia processed in one case of spasmodic torticollis. These kinds of side effects mostly occurred after 3 – 7 days of injection (the earliest occurred at the day of injection). Almost all disappeared naturally at 2 – 9 weeks. There were 2 cases drop of mouth angle lasted for 20 weeks, it was probably because the injection was did at musculus quadratus labii superioris; ii) most patients processed local rigid and uncomfortable feeling at the same time as disappearance of spasm, the duration attained 10 – 12 weeks; iii) only 1 case processed systemic forceless at the second day after injection, and the side effect naturally disappeared after 1 week. Among 41 cases of either first or supplementary injection, all had no allergic reaction.

Discussion

Dystonia refers to the extrapyramidal disease which characterized by over contraction of agonistic muscle and antagonistic muscle that expressed as involuntary movement and abnormal postures. According to the causes of disease, it is classified into primary and secondary types. Primary type is divided into holotonia type and topical type. Topical type includes spasmodic torticollis, blepharospasm, laryngospasm, lateral facial spasm, Meige's Syndrome, etc. Secondary type includes: i) hepatolenticular degeneration; ii) pallidal globus melanin degeneration; iii) calcification of bilateral basal ganglia; iv) initiated by psychotolytic drugs. According to age of first onset classified into: i) Children type: 0 – 12 years; ii) teenager type: 13 – 20 years; iii) adult type: after 20 years.

The cause of disease and onset mechanism of primary type are not known, CT and MRI scan have no abnormality. In these years, it is thought that the cause is the disarrangement of noradrenaline that leads to over active of cholinergic system. Wooten *et al* discovered that the dopamine β-hydroxylase (DβH) level of blood plasma of autosomal dominant inheritance patients is higher than that of autosomal recessive inheritance patients and normal people. The DβH peripheral synthesis is under control of central nervous system. Over activity of sympathetic nerve or central control sympathetic nerve system usually leads to increase in circulated DβH.

Dystonia mainly affected striated muscle, some parts are more easily to be involved, e.g. orbicular muscle of eye, sternocleidomastoid, trunk muscle, pronator of limbs, flexor muscle of toe, contractor muscle of plantar. The clinical characteristics are strange involuntary movement and slow and stressful contraction of far-end muscles of limbs and trunk muscles which leads to special postures, e.g. involuntary squeeze and closure of eyes, convulsion of face muscle, torticollis, etc. There is no regular

pattern of episode, the time intervals are not the same. In the early stage, the symptoms only occur during activities and disappear when sleep. In the later stage, the episode tends to be stable. The states of illness show a progressive development pattern. For the children type, the first onset is usually abnormality of gait, usually develops into systemic type. Adults usually onset at hands, face and trunk, only 18% develops into systemic type.

Because the causes of disease and onset mechanism are not known, the primary dystonia has no special therapy until now. From 1980, BTXA treatment is used and the curative effects are good and safe. BTXA is a very strong exotoxin produced in anaerobic environment by botulinum bacteria. According to the difference of toxicity and antigenicity, it is classified into A-G types. BTXA is easily to crystallise into standard conditions. Animal tests stated that local injection of BTXA can produce characterised muscular atrophy and loss of nervous control, but most of this action is reversible. The action of BTXA is to inhibit release of acetylcholine thus leads to temporal forceless of striated muscle, but does not cut the nerve excitation conduction. Clinically, local injection of BTXA can make energy between muscles to attain new balance through relief of muscle spasm thus leads to improvement of a series of symptoms related to muscle spasm. After injection of low dosage of BTXA into local muscle, the toxin quickly combines with muscle, the entire part enters circulatory system, and the BTXA is eliminated quickly in blood, so is not easily to be isolated from blood. Only when there is a high density of BTXA in blood can it be possible to enter blood-brain barrier. The fatal dosage of human is 2500 – 5000U. Up till now, documentations reported that this treatment do not have any severe or systemic side effects, duration of each treatment is about 1 – 6 months. The improvement of clinical symptoms is determined by its degree of sealing towards neuro-transmitter of nerve-muscle joint.

Many studies proved that BTXA showed unique advantages in treatment of spasmodic dystonia. It is safe, easy to operate and with high efficacy, easy to be used clinically. But many patients need replicated injection to maintain curative effects, so it needs to be further studied on its long term effects and immune response.

Toxin Type A has strong toxicity, is stable and easily to be produced. It has been proved as a safe and effective biological formulation by animal tests clinically. Botulinum Toxic (BTX) selectively actions at surrounding cholinergic nerve endings, inhibits excitation and primary quantum release of acetylcholine, the action is strongest at nerve muscle joints and generally cannot pass through blood-brain barrier.

It makes muscle relax and paralyze, thus eyelid and face muscle spasms can be improved[3,4].

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