Botulinum Toxin A in the Treatment of Dystonia: a Clinical Analysis of 409 Cases

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Abstract

Objective: To study the efficacy and safety of botulinum toxin A (LANTOX) injection of the treatment of dystonia.

Method: The involved spasm muscles of dystonia patients were locally injected with LANTOX. The efficacy and side effects were compared before and after injection.

Result: Among the 409 cases of dystonia treated with LANTOX, there were 175 cases of facial spasm, 63 of blepharospasm, 40 of Meige syndrome, 37 of cerebral palsy, 34 of spasmodic torticollis, 31 of tension headache and 29 of post-stroke muscle spasticity. The total effective rate was up to 99.3%. The initial effects were obtained 4 hours to 3 days after treatment. The remission time of myospasm symptoms and sign was averagely 7 months. The local side effects were mild and transient.

Conclusion: The local injection of LANTOX is safe, effective and simple for the treatment of the patients with dystonia, with mild and reversible side effects.

Key words: dystonia/ medical treatment, Clostridium botulinum toxin, type A/ therapeutic use, Clostridium botulinum toxin/ side effect

Introduction

Dystonia is a kind of difficult-to-treat syndrome and commonly found in neurology clinic. Since 1979, an American Dr. Scott firstly success in the treatment of strabismus by using botulinum toxin type A, BTX-A local injection[1], this treatment method has been applied into the treatment for many kinds of dystonia[2-4]. Our department used Chinese product LANTOX injection to treat these kinds of patient total 409 cases for 5 years, follow up visit 6 – 20 months, with satisfactory result.

Subject and Method

1. Design

Diagnostic-based vertical observation study.

2. Venue and Subject

In March 1998/ March 2003, our neurology department received about 500 cases patient of LANTOX injection treatment of dystonia, statistical data shown patient with at

least one follow up visit, total 409 cases. Male 167 cases, female 242 cases; age 18 – 76 years old, average aged 45.5; clinical history 6 months – 20 years. Including hemi-facial spasm 175 case (left side 83 cases, right side 92 cases), blepharospasm 63 cases (double side 27 cases, left side 17 cases, right side 19 cases), Meige syndrome 40 cases, cerebral palsy stimulated spasm 37 cases, spasmodic torticollis 34 cases, tension headache 31 cases, post-stroke spasmodic hemiplegia 29 cases. All of the received patients were without fever and acute inflection, all of them did not feel satisfactory from long-term medical treatment, physiology therapy, acupuncture and moxibustion, sealing, thread yarn, surgery treatment and etc., among them three cases with facial spasm were re-attacked one year after microvascular decompression. Except the post-stroke group and cerebral palsy group, 76 cases were operated with skull CT and MRI inspection, 94 cases were operated with electroencephalogram, 147 cases had been determined their liver, kidney function and blood and urinary routine, all being normal.

3. Method

Treatment method: The medicine used is LANTOX for injection manufactured by Lanzhou Institute of Biological Products, Ministry of Health, People Republic of China, stored at -5℃ ~ -20℃ freezer. Reconstitute to required concentration by 9 g/L sodium chloride injection solution during use (normally 25U/mL or 50U/mL), it should be completely used within one hour after reconstitution (should not more than 4 hours). Hypersensitive person, pregnant, person with acute and difficult-to-control disease and serious heart, liver, kidney and etc. serious organ dysfunction are prohibited to use. Injection method was based on individual-status principle, diagnosis in specialist clinic before treatment; avoid taking any other drug during treatment. For patient whose injection site was difficult to locate (especially injection at neck), galvanopuncture location method could be used (using galvanopunture meter); deep muscle could be injected under normal EMG guidance (electromyography of spasm muscle show continuous or discontinuous muscle rigidity myo-electric behavior). Patient would take a sit-down or lay-down position, used of 1 mL syringe, number 4.5 or 5 needle, for deep muscle of podosoma, number 6 or 6.5 needle could be used, hypodermically or intramuscular injected 2.5 – 7.5 U for each site. Injection site(s) and dosage were according to the size, amount, and spasm status of muscle, and treatment result. Used of multi-injection method, strictly prohibited to inject into blood vassal, the separation distance between every injection sites was normally 2 – 4cm. For the poor treatment result, re-injection would be taken 1 week after the last injection. The separation time for recurrent patient's treatment should be 4 – 8 months after last treatment.

4. Data Collection Method

Using united record form detail recorded muscle spasticity, on-set time, time taken to the best effect, effect duration and side effect before and after treatment. If there was no special case, injector follow up visit would be done in-present or by phone after injection, within 1 week, 1 months, 3 months, half year and 1 year.

5. Evaluation Standard

Treatment evaluation standard: hemi-facial spasm and blepharospasm were graded according to Cohen standard[5], spasmodic torticollis was scored according to Tsui scale[6], the changing of spasmodic dystonia was scored according to modified Ashworth scale[7], improvement of spasticity last at least for 4 weeks would be considered as effective.

6. Clinical Efficacy Evaluation

Tsui scale score decrease 10% after treatment would be considered as no effect, decrease 11% - 50% would be considered as improved, decrease 51% - 80% would be considered as obviously improved, decrease 81% - 100% would be considered as completely relief; Cohen and Ashworth scale score decrease to Grade 0 or 0 score would be considered as completely relief, decrease $\geq$2 grade or $\geq$9 score would be considered as obviously improved, decrease 1 grade or 4 -8 score would be considered as partial improved, without de-graded or <4 score would be considered as no effect. Meige syndrome, tension headache and other kind of local dystonia and local muscle tonus were evaluated according to patients' objective feeling and subjective inspection considered as completely relief, obviously improved, partial improved and no effect. Recurrent standard: spasticity increased $\geq$ 1 grade or $\geq$4 score.

7. Major Result Observation Standard

Efficacy; function.

Result

1. Efficacy

LANTOX normally started to effect at 4h – 3d after injection, it reach the best treatment result at week 1, 2, average 9 days, effect duration normally 3 – 11 months, average 7 months, total efficiency 99.3%. Among them, two cases of spasmodic torticollis taken carbamazepine for 6 months after LANTOX injection, follow up for 2 years without recurrent. During the treatment of blepharospasm and facial spasm, it was separated into middle age and elder, cosmetic wrinkle removal effect was recorded. For

observed recurrent patient, the spasticity was lesser than before treatment, dosage of re-injection was same as or slightly more than the first time injection, efficacy was no change. The relief status in the treatment of 7 kinds of dystonia see following table.

Table 1 Efficacy of LANTOX in the treatment of 7 kinds of dystonia (n/%)

Kind of disease	n	Completely relief	Obviously relief	Partially improved	No effect
Hemi-facial spasm	175	116/66.3	54/30.9	5/2.8	0
Blepharospasm	63	52/82.5	8/12.7	3/4.8	0
Meige syndrome	40	29/72.5	11/27.5	0	0
Cerebral palsy (spasmodic)	37	3/8.1	26/70.3	8/21.6	0
Spasmodic torticollis	34	18/52.9	16/47.1	0	0
Tension headache	31	19/61.3	7/22.6	2/6.4	3/9.7
Post-stroke spasm	29	13/44.8	16/55.2	0	0

2. Side Effects

409 cases after injection did not obtain any allergy reaction and serious toxic side effect, local side effect was slight and temporary. Among them, 3 cases obtained acupuncture syncope reaction (dizziness, pale), 27 cases after injection obtained slightly local swelling or pain, 9 cases obtained local spot-like blood spot, 165 cases obtained slight askew of labial angle, 23 cases obtained slight non-complete closure of eye lid, 1 case of epiphora, 4 cases neck muscle weakening, 1 cases felt tightening at root of nose, 2 cases of arm weakening, there were being normal after 2 – 3 weeks without any special treatment. Neither difficult swallowing nor drinking cough was reported.

Discussion

The inhibition of neuro-function of LANTOX was temporary, after reconstruction of motion end plate, neurotransmission and muscle contraction would be recovered, the side effect was also temporary, re-injection was also effective. In nowadays, this treatment method is applied in many kinds of dystonia treatment with different dosage and method, side effect is not rare to obtain[8 -10].

In this treatment group, used of LANTOX to treat 175 cases of facial spasm, 63 cases of blepharospasm, 40 cases of Meige syndrome, 37 cases of cerebral palsy (spasmodic type), 34 cases of spasmodic torticollis, 29 cases of post-stroke spasm, efficient

reached 100%. 31 cases of tension headache, efficient also reached 90.3%. Efficacy average lasted for 3 – 11 months. In this group of cases, neither systemic botulinum toxin poisoning nor allergy responds was reported. Side effects mostly occurred when the symptoms were begun to improved, local side effect was slight and temporary, and all of them were recovered spontaneously. According to other report, LANTOX did not effect on some dystonia treatment which called resistance phenomenon, patients with this phenomenon were divided into two situations, one was did not effect during the first time injection, called idiopathic resistance, the other one was LANTOX do effected at the beginning of treatment, but became non-effective after many times of treatment, called discontinues resistance, incidence was 5% - 10%. The reason of inducing idiopathic resistance was not clear, discontinues resistance was mostly due to the LANTOX antibody generated in patient's body, then it induced drug resistance to the drug, it reduce the treatment efficiency[1].[2]. There was no report of obvious resistance to the drug in this treatment group, excepted 3 cases of no effect in the treatment of tension headache, the others, 406 cases were effected, there were 85 cases of patient with more than 5 times re-injection, 100% efficient, it was not consist to literature report, the reason was not clear, it could be further study. In this article, we speculated that the different in efficacy and rare to obtain serious side effect may due to following reasons:

1. Reconstitution Method

It should be used within 4h after reconstitution, incorrect reconstitution method may cause denature of toxin resulting in effect on the efficacy.

2. Injection Method

Method and dosage should be personalized; operator should understand functional anatomy of every local muscle, select suitable muscle for injection, use of multi-site injection. For deep muscle, operator with less experience or difficulty in site location, it is recommended to operate with electromyography guidance or galvanopuncture location method[13]. Operator should base on the spasmodic muscle size, location and amount to decide the concentration of LANTOX. For the injection of large size muscle, it could inject at the same time of needle withdrawal, as a result, the drug could be widely spread. The injection site(s) and number of points should be carefully considered, too much or too few could effect on the efficacy. It is valuable to remind that orbicular muscle of eye is exterior and thin; syringe needle should slanted insert to skin, form a skin mound with 0.5cm diameter at appropriated injection site is suggested; injection dosage for sternocleidomastoideus should not be too much, accuracy point location, injection should not too deep, avoid too much injection sites,

it should be conduct with torticollis motion related assisting muscle injection (double side injection is required if necessary), for female and/ or small neck size, it should reduce injection dosage, noted that the needle direction is suggested to slant outside during injection, it could reduce the spread of toxin into nearby guttural muscle, hence avoid the occurrence of difficult swallowing.

3. Noted Item

Patient with fever, acute inflection, blood disease etc. situation should temporary avoid injection. In this treatment group, 3 patient cases were injected when empty stomach or tired, all reported dizziness, pale etc. acupuncture syncope reaction, therefore patient with empty stomach or tired should not be injected, in order to avoid acupuncture syncope. It should regularly prepare epinephrine to avoid any accident breaks out, hospitalize after injection for observation in a short period. It is said that the efficacy of LANTOX could be reinforced by aminoglycosides antibiotics or other drugs that inference of neurotransmission, therefore patient using the above drugs and patient attacked by myasthenia gravis, Lambert-Easton syndrome and motor neuron disease should be handled carefully. In the view of this article, strict operation guideline and good handling of appropriated dosage and separation time for re-injection were important; although unsatisfactory result has turned out, it should not conduct re-injection many times in a short period.

Conclusion

LANTOX treating dystonia is a safety and effective, easy to operate non-surgery treatment method. The operation is recommended to operate under electromyography guidance at the beginning of the study in this technology. It is the effective way to guarantee efficacy and reduce side effect.

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