Correlation between Clinical Response and Dosages of Botulinum Toxin A in Treatment of Spasmodic Dysphonia

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Abstract

Objective: To explore the appropriate dosage of botulinum toxin A (LANTOX) in treating spasmodic dysphonia (SD).

Method: The LANTOX is obtained from Lanzhou institute of biological products. All patients were randomly divided into 5U and 10U groups and treated with percutaneous unilateral thyroarytenoid muscle injections with EMG guidance. They were followed up at least 6 months. Remission rate, duration of efficacy and the kinds, severity and duration of the side effects on both groups were observed. The degree of spasm is evaluated by Blitzer rating scale.

Result: Over past 5 years, 27 patients with adductor type SD were treated, total 79 injection sessions. 18 cases are focal laryngeal dystonia (FLD) and 9 cases are accompanied with segmental dystonia (SDT). 38 sessions used 5U group (92%) with comparing 39 injections in high dose group (95%). The average duration of benefit are 12.9 and 16.8 weeks respectively ($P<0.01$). The adverse effects such as harsh voice occurred 18 sessions (44%) and 10 sessions (26%), and dysphagia occurred 10 sessions (24%) and 6 sessions (16%), (both $P>0.05$). All the adverse effects completely disappeared in 2 – 6 weeks. No patients in our study suffered from anaphylaxis or systemic intoxicity.

Conclusion: Unilateral thyroarytenoid muscle topical LANTOX injections with EMG guidance is a safe and effective treatment for adductor SD. The average duration of benefit appears longer in 10U group than in 5U group. It is worthwhile to further exploring how to improve benefit, prolong the duration of benefit and decrease adverse effects.

Key words: Spasmodic dysphonia; Botulinum Toxin A; Treatment

Spasmodic dysphonia (SD), also called focal laryngeal dystonia (FLD), is a chronic nervous system disease caused by disturbance in central motor messages interpretation process, characterized by vocal fold spasm caused by speaking, which expressed in form of spasmodic pronunciation during speaking[2]. Internationally, in the recent 10 years, local injection of Botulinum Toxin A (BTX-A) in treatment of adductor type SD obtained 97% remission, and generally acquainted as the first choice of treatment[3]. In the nation, there were authors who tried this method and obtained certain satisfactory results[4], but the suitable dosage and result of LANTOX application on citizens was not reported. We randomly divided the 27 cases and 79 sessions we had in the past 5 years into 5u group and 10u group for comparison, processed percutaneous unilateral thyroarytenoid muscle injections with EMG guidance. The results are as follows.

Information and Method

1. Clinical Information

The cases were collected from our hospital the in and out patients of neurology department of internal medicine, ear-nose-throat – cephalocervical surgical department from June 1996 to June 2001. Accurate diagnose adductor SD 27 cases, male 11 cases, female 16 cases, aged from 25 – 68 years (38.4 ± 17.1); medical state 0.5 – 16 years (5.6 ± 4.1). 18 cases were focal laryngeal dystonia, 9 cases were accompanied by segmental dystsonia, all were adductor type. 2 cases had family history of adult onset type dystonia, all expressed as SDT; after at least 3 months of oral taken rivotril, lorazepam, haloperidol, artane, carbamazepine (2 oral types) and local blocking, physiotherapy, acupuncture and moxibustion, pronunciation training but no effect observed.

2. Treatment

I) Diagnose standard: (i) Clinical expression of typical spasmodic pronunciation during speaking, some of pronunciations were recorded. (ii) Nervous system somatoscopy and cranial CT or / and MRI examination (except the central) for the progressive organic disease, ear-nose-throat examination except local organic disease and neuromuscular paralysis. (iii) Fiberoptic laryngoscope examination for vocal fold spasm and differentiated adductor and abductor types, some of images recorded.

II) Random, double-blind, contrast and prospective designs were used for each session of patients to divide into 10u group and 5u group. After treatment of 2 weeks, estimated each week, at least for 6 months. Remission rate, duration of efficacy and the kinds, severity and duration of the side effects on both groups were observed.

III) Medicine used and methods: the medical used was BTX-A for injection produced by Lanzhou Institute of Biological Products [(97)Drug Approval(Lan) S-01], which was in form of lyophilized crystal, diluted to 2.5u/0.1ml by saline before use. The patient lied in supine position, the neck had enough space to extend; hollow special myoelectic electrode with external insulated coating was used, the lateral pole was connected to the electromyograph, the posterior side was connected to the injector; injected into lateral thyroarytenoid muscle through skin and diaphragm under myoelectric guidance.

IV) The severity was defined according to standard of Blitzer[1]: 1 = normal, 2 = light, 3 = light / medium, 4 = medium, 5 = medium / serious, 6 = serious, 7 = very serious

V) Therapeutic evaluation: completely remission: degrade to level 1; obvious remission: degrade 4 levels or above; partially remission: degrade 3 levels or below; no effect or get more serious: no degradation or get more serious.

VI) Use PSP software package for statistics.

Result

There were 27 cases matched the diagnose standard of adductor SD, all processed difficult spasmodic pronunciation during speaking, looked suffocated and panting, 23 cases accompanied broken pronunciation, 17 cases with different levels of throat spasmodic painful; 16 cases found by fiberoptic laryngoscope with obvious shivering of vocal fold; 5 cases found 4-8hz shivering from electromyogram; 2 cases found by CT and/or MRI subcortical cavity space infarction.

Comparison of clinical information of 5u and 10u group of LANTOXA treatment of 27 cases, 79 sessions was shown in Table 1:

Table 1 Comparison of clinical information of 5u and 10u group of LANTOX treatment

	Sessions	F / M	Age	Medical state (Yr)	SDT	More than level 4
5u group	38	15 / 23	38.1±16.3	5.4±4.0	16	36
10u group	41	16 / 25	38.1±17.7	5.8±5.2	18	40
P value		> .05	>.05	>.05	>.05	>.05

After t test of the measurement data and X^2 test of the enumeration data, there was no statistical significant for the index variance between the 2 groups. The 2 groups were comparable.

Local injection of LANTOX in treatment of SD is heteropathy. Recurrence often occurs and needs reinjection. The cases of our group accept 1 – 9 sessions of treatment. The comparison of the effectiveness and side effects of the 2 groups was shown in table 2:

Table 2 The comparison of the effectiveness and side effects of the 2 groups

	Sessions	Completely remission	Obvious remission	Partially remission	No effect	Duration of effectiveness (week)	Harsh voice	Dysphagia
5u group	38	35	2	0	1	12.9±5.1	10	6
10u group	41	39	1	0	1	16.8±4.3	18	10
P value		>0.05	>0.05	>0.05	<0.01	>0.05	>0.05	>0.05

All cases showed effectiveness after 10 – 24 hours of treatment, and attained the highest level at 5 – 7 days; the complete remissions of the 2 groups were 92% and 95% respectively. Each had 1 session with no effect due to failure of injection (complete remission after successful injection 1 week after). Average duration of effectiveness of the 10u group was 4 weeks longer than that of 5u group.

Side effects of harsh voice and dysphagia of each group were 26% and 44%, 16% and 24% respectively, but the variance did not attain statistical significant. The side effects were obvious 3 – 10 days after injection, started to recover after about 2 weeks, complete recovered after 4 – 6 weeks. Total 7 sessions of the two groups showed partially or throat pain, last for 1 – 3 days; one case had blood in sputum; no general allergy or toxic reaction.

Discussion

Although the etiology of the SD was still in argue, there are more and more evidences indicate that it is a chronic nervous system disease caused by a disturbance in central motor message interpretation progress. Some of the expression in cases classified in FLD and SDT, the 9 cases merged with SDT also supported this point of view. For the SD diagnose, one should have sufficient knowledge for the disease and correct the misconception in mental diseases. The expressions of adductor type SD were suffocated-like during speaking, tension-like spasmodic pronunciation, sound difficult and hard, usually accompanied by vibrated tone, and inappropriate chopping pronunciation and glottal fry, some accompanied by different levels of spasmodic

pressured-like pain of throat; the symptoms are lighter at the beginning of speaking, and get more serious during speaking; the factors that can temporally improve the symptoms include wake up in the morning, after drinking of alcohol, stop speaking for some rest, make use of "sensory tricks" (e.g. yawning and loud laughing); the factors that can worsen the symptoms include nervous emotional, facing of telephone, microphone or many audiences; most of the patients had normal pronunciation when laughing or singing. Abductor type expressed as difficulties in speaking, forceless pronunciation with breath, usually suddenly stops or pronounced bass segments. The diagnose and classification need fiberoptic laryngoscope examination, adductor type expressed as vocal fold catalepsy adduction caused by spasm mainly involved thyroarytenoid muscle during speaking; abductor type expressed as vocal fold catalepsy abduction caused by spasm mainly involved thyroarytenoid muscle. Identification of each type is essential because the method, muscle and dosage of LANTOX injection are all different.

Before the application of LANTOX, there was no satisfactory treatment for SD. Although cut of recurrent nerve can dramatically remiss the symptoms, but only 36% still have improvement after 3 years, 1/33 cases sustain normal pronunciation[5]. LANTOX is a nervous toxin produced by Botulinum Bacteria, with reaction of zinc endopeptidase, combines with synaptic nerve cell receptors of motor muscle joints at injection sites, enters cells through internalization of energy, acts on the related protein of synapse, inhibits release of acetylcholine, leads to a more durative paralysis of muscle, thus remises muscle spasms. In 1989, Brin firstly reported successful treatment of adductor type SD by percutaneous unilateral thyroarytenoid muscle injections with EMG guidance, which provided an effective new treatment for the disease.

The ways to report treatment of adductor type SD by LANTOX injection into thyroarytenoid muscle were different. Classified by the ways of injection, there are transnasal or peroral injection and percutaneous myoelectric guidance injection, remission of symptoms were 100% and 80%. There were no obvious differences in dosage, duration and side effects. According to the lateral side of thyroarytenoid muscle injection there were unilateral and bilateral injection, compare for equal dosage, the improvement of symptoms and duration were similar, but the latter processed more dysphpagia and the duration was longer[8]. The comparison between different dosages of unilateral injection was not reported, we used unilateral thyroarytenoid 10u and 5u dosage for random correlation analysis, duration was 10 – 24 hours after treatment, attain the highest value at 5 – 7 days. The complete

remission was 92% and 95% respectively, the average duration of 10u dosage was 16.8 week, whereas 5u dosage was 4 weeks. The results were similar to the 89.7% and 15.1 weeks reported by Blitzer.

Side effects occurred 1 – 2 days after curative effects, usually processes harsh voice and dysphagia, for the 2 groups, the percentages were 26% and 44%, 16% and 24% respectively. The 10u group seemed to have a higher percentage, but no significant values obtained, and was similar to the 35% harsh voice and 15% dysphagia[1]. Normally the conditions were improved at around 2 weeks, completely recovered at 4 – 6 weeks, none of the cases needed nasal feeding and endotracheal intubation or incision. No general allergy or toxic reaction.

In conclusion, treatment of adductor type SD by percutaneous unilateral thyroarytenoid muscle injections with EMG guidance was safe and effective. Compared 10u and 5u dosage of unilateral injection, the curative effects were similar, average duration was extended, no obvious increase of side effects. How to increase the curative effect, maximize quality of pronunciation, extend the duration and decrease the side effects worth profound investigation.

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