Low Dose Botulinum Toxin A for Treatment of Spasmodic Torticollis: A Randomized and Controlled Clinic Trial

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Abstract

Objective: To compare the efficacy, duration of benefit and adverse effect between high and low dose botulinum toxin A (LANTOX) in treating spasmodic torticollis (ST).

Method: The LANTOX is obtained from Lanzhou institute of biological products. All patients were randomly divided into high concentration (25U/ml) and low concentration (17U/ml) groups and treated with topical LANTOX injections with EMG guidance. They were followed up at least 6 months. The 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 Tsui rating scale.

Result: 126 patients with ST were treated over past 3 years. 72 were female and 54 were male. They aged from 25-75 (44.26±13.86) with the course ranging from 1-25 years (5.73±15.48). 103 cases are focal ST and 23 cases are accompanied with segmental or multifocal dystonia. There were 65 cases in high dose group and 61 cases in low dose group, the effect rate is 87.69% and 86.89% ($P>0.05$), and the average duration of benefit is 16.98±6.19 and 16.63±5.17 weeks ($P>0.05$), the therapeutic dosage is 31U ± 65U and 253U±98U ($P< 0.05$). The adverse effects such as neck weakness occurred 13.84% and 11.47%, while dysphasia occurred 9.24% and 8.2% (both $P>0.05$). All the adverse effects completely disappeared in 2-6 weeks. There were 4 cases and 2 cases respectively had general fatigue and weight loss which lasted 0.5-3 years.

Conclusion: Topical LANTOX injections with EMG guidance is a safe and effective therapy which can be considered as the first choice for ST. The Therapeutic efficacy can be maintained with LANTOX preparation of low dose with equal volume. Whether the preparation with lower dosage can decrease the adverse effects need further exploration.

Key words: Spasmodic Torticollis; Botulinum Toxin A; EMG; Treatment

Spasmodic Torticollis (ST) manifests continuous or paroxysmal involuntary spastic contraction of neck muscles. Sustained turning, tilting, special malformation of head, neck and shoulder, can result in. There is poor response to previous oral drugs or physical therapy. Fortunately, about 80% ST patients successfully respond to topic

injection of botulinum toxin A (LANTOX) [1]. As neck muscles are more bulky than that of face and eyelids, we hypothesize whether diluted LANTOX encourages drug diffusion in the muscles, and then improves efficacy and the dose of LANTOX could be tapered down. 126 ST patients were enrolled a randomized and controlled clinic trial and treated with LANTOX (100units/ampule) which diluted in to 4 ml and 6 ml respectively.

Material and Method

1. Material

126 patients with spasmodic torticollis were enrolled at neurology department from March 1998 to May 2001. There were 54 males and 72 females aged from 25 to 75 (mean 44.26±13.86). Their course of illness ranged from 1 5to 25 years (mean 5.73±15.48). 103 cases only had focal ST and other 23 patients accompanied with segmental or multifocal dystonia. All patients had failed to get substantial response from at least two drug administrations (such as artane, clonazepam, myonal, baclofen, carbamazepine and haloperidol) or intolerable to the side effects of these drugs. Patients were ruled out if they had undergone previous thalamotomy, myectomy, or surgical denervation procedures. Furthermore, drug induced dyskinesia (acute or tardive dyskinesia) and other secondary cervical dystonia (such as Wilson's disease) all meet the exclusion criteria.

2. Method

Design: The 126 patients were randomly assigned to two groups. One group accepted routine concentration LANTOX (25U/ml) and the other administrated diluted LANTOX (17U/ml). We prospectively compared the efficacy, duration of benefit and rate of side effects between two groups. All patients were evaluated two weeks before and after the treatment, and then were followed up monthly at least six months.

Dosage and Administration:

2.2.1 LANTOX is obtained in a pure crystalline form from Lanzhou institution of biological products. Each ampoule contains 100 units toxin. Prior to use, the toxin was dissolved in 4 ml or 6 ml normal saline to a concentration of 25U/ml or 17U/ml.

2.2.2 The cervical muscles were selected for LANTOX injections if we found (1) the functional muscles contribute to the certain abnormal position of patient's head and neck; (2) the hypertropic and dystonic contractive muscles by observation or palpitation; (3) patient's complaints of aching muscles.

2.2.3 All patients underwent topic injections of LANTOX with EMG guidance. We used

a special hollow EMG needle (14R18 or 13R19) with lateral pole connected with EMG and posterior pole connected with syringe. Dystonic contraction is defined as presentation of continuous or paroxysmal bursting contraction pattern.

2.2.4 The sites and doses of each neck muscle are mentioned as follow. (1) Five points on sternocleidomastoid muscle (3 points on upper2/3 portion with 0.5ml at each point, one point with 0.3ml at the end of sternal bone and one point with 0.3ml at eh end of clavicle bone). (2) Eight points (0.3ml each) on trapezious muscle. (3) Five points on splenius capitus muscle (0.5ml each). (4) Five points with 0.5ml each on posterior deep muscles of the neck (longus capitis muscle and semispinalis capitis muscle). (5) Four points on scalenus muscle (0.3ml each). (6) Three points on levator scapulae muscle (0.3ml each).

Evaluation: Evaluation was performed according to Tsui scale [2]. Percent response= (T0-T1)/T0. (T0 equals pre-therapy Tsui score, and T1 equals post-therapy Tsui score). The percent response falls >85%, 51-85%, 26-59%, and <25% stands for complete remission, marked remission, partial remission and no improvement respectively. Effective rate= (complete remission + marked remission)/total number of treatment.

Statistical analysis administrated PSP software package.

Result

126 patients were definitely diagnosed as ST and were enrolled. They were randomly divided into two groups to accept topic injections of LANTOX which were diluted to 25U/ml and 17U/ml each. The clinic features of both groups are listed in table 1.

Table 1 Comparison of the 126 patients' clinic features between the two groups

	Cases	Male/Female	Age (years)	Course of illness	SDT	Tsui score
High dose	65	28/37	43.84 ± 13.83	5.68 ± 14.98	13	14.58 ± 1.80
Lose dose	61	26/35	44.7 ± 13.71	5.82 ± 15.21	10	14.82 ± 1.78

There was no significant difference between the two groups by t test and chi-square test.

The comparisons of efficacy and side effects of two groups are listed in table 2.

Table 2 Comparison of efficacy and side effects between two groups

	Cases	Complete remission	Marked remission	Partial remission	No improvement	Duration of benefit (weeks)	Neck weakness	Dysphagia	Dose(U) of injection	Number muscles
High dose	65	37	20	6	2	16.98 ± 6.19	6	6	331 ± 65	5.86 ± 1.84
Low dose	61	34	29	6	1	16.63 ± 5.17	7	5	253 ± 98	6.12 ± 1.88

The dosage of the two groups had significant difference ($t=4.85$, $p<0.01$), and the other issues had no significant statistic difference.

On both groups, the effect emerged 5-10 days after treatment and reached peak in two weeks. After treatment, the Tsui scores of the two groups were 3.32±3.58 and 3.68±3.63 respectively, and the decrement of Tsui scores of the two groups had no significant difference ($t=1.37$, $p>0.05$). The effective rate was 87.69% and 96.89% each. The mean duration of benefit was around 16 weeks. There were 19 cases (9 cases and 10 cases in each group) had no relapse in 0.5-3 years.

Neck weakness occurred 13.84% and 11.47%, and dysphasia occurred 9.24% and 8.2% in the two groups respectively. But there was no significant difference. These two side effects were most obvious during 3-10 days after the LANTOX injection, and began to recover two weeks later, and completely recovered in 4-6 weeks. Two cases had transient (30 minutes) red macula around the injection site. But no anaphylactic shock followed. Poor appetite, fatigue and weight loss were complained by four and two cases in high-dose and low-dose groups respectively. The former two side effects lasted 2-7 weeks, but weight loss persistently remained.

Discussion

ST is a kind of chronic central nerve system disease with disturbed motor message processing sequence. It might be the only manifestation of focal dystonia at neck or a partial manifestation of segmental, multifocal or generalized dystonia. Excluding some secondary dystonia caused by inherited or drugs, the cause of ST remains unknown in the majority of cases. Now LANTOX topic injection has been considered to be the first choice for treatment of ST. LANTOX is a kind of zinc endopeptidase which cleaves the translocation protein SNAP-25 (synaptosome associated protein) and blocks release of acetylcholine at neuromuscular junction and causes muscles relaxation.

We particularly concerned how to enhance efficacy and minimize side effects. There are two major factors that affect the efficacy: location of involved muscles and accurate intramuscular injection. EMG guidance is helpful not only to find the involved muscles but also to assure the LANTOX is delivered into the dystonic muscles. Increased magnitude of benefit and decreased occurrence of side effects were reported by a randomized cross-controlled trial and a randomized, double-blinded and controlled clinic trial [1,3].

Because neck muscles are larger than that of face and eyelid, is it helpful to increase magnitude of benefit or decrease the dose of LANTOX if we administrate lower concentration of LANTOX. In this clinic trial, we treated the two groups with different concentration of LANTOX (25u/ml and 17u/ml respectively). Because the injection sites and the volume of LANTOX solution for each site are same in the two groups, the group using higher concentration solution accepted high dose LANTOX while the other group accepted low dose LANTOX. The result suggested that the dose of LANTOX was tapered down about one fourth while the effective rates were nearly same between the two groups (86.89% in low dose group and 87.69% in high dose group). The mean duration of benefit was all about 16 weeks. The rates of side effects such as neck weakness and dysphagia were about 10%. The rates of efficacy and side effects in our trial are similar to the previously reported 80% of effective rate and 9% of side effect rate. [4]

There were 4 patients in high dose group and 2 patients in low dose group that suffered from fatigue and weight loss. The symptom of fatigue improved in 2-7 weeks, but the weight loss remained (follow-up 0.5-3 years). Weight loss easily occurred with the conditions of multiple injection sites, high dose, and patient with symptomatic dystonia. The probable mechanism contributes to generalized toxin dispersion and presynaptic inhibition at neuromuscular junctions. [5] Dysphagia and neck weakness are two major side effects (10%). The problem affects not only food intake but also easily causes asphyxia probably. The possible mechanism is direct infiltration of toxin to the posterior pharyngeal muscles or esophageal muscles. We should avoid excessive deep injection, high dose of LANTOX, and bilateral injection for sternocleidomastoid and scalene muscles in one time. When the side effect occurred, semi-supine position and soft food are beneficial for swallowing. Nasal feeding is suggested if severe.

In conclusion, topic LANTOX injection with EMG guidance for the treatment of cervical

dystonia is safe and effective. It is worthwhile to explore whether lower concentration or lower dose of LANTOX for treating ST can maintain therapeutic benefit and decrease side effects.

References

1. Hu XY, Shao YQ, Wang *et al*. Local Injection of Botulinum Toxin Type A for Cervical Dystonia under Electromyography Guidance: A crossover controlled clinical trail. J Clin Neurol, 1999, 12 (4): 236–7.
2. Green P, Kang U, Fahn S, *et al*. Double-blind place-controlled trail of Botulinum toxin Injections for the treatment of spasmodic torticollis. Neurology, 1990, 40:1213.
3. Gomella CL, Buchuman AS, Tanner CM. Botulinum toxin injection for Spasmodic torticollis: Increased magnitude of benefit with electromyographic assistance. Neurology, 1992, 42:878.
4. Brans, -J-W; de-Boer, -I-P; Aramideh, -M; *et al* Botulnum toxin in cervical dystonia: low dosage with electromyographic guidance. J-Neurol. 1995; 242(8):529-34.
5. Bhatia, -K-P; Munchau, -A; Thompson, -P-D; Houser, -M; Chauhan, -V-S; Hutchinson, -M; Shapira, -A-H; Marsden, -C-D Generalised muscular weakness after J-Neurol-Neurosurg-Psychiatry. 1999 Jul; 67(1): 90-3.
6. Schantz EJ, Johnson EA. Properties and use of botulinum toxin and other microbial neurotoxins in medicine.

(Originally published in Microbiol Rev, 1992; 56(1):80-99)