Botulinum Toxin A in the Treatment of Parkinson's Disease Patients with Superior Extremities Muscle Rigidity Spasmodic Tremor-Random, Double-blind, Placebo-Control Test

Zhan Peiyuan, Wang Lijuan, Zheng Zhiping, Mai Xunliang, Wang Xiang
(Department of Neurology, Guangdong Provincial People's Hospital, 510080)

Objective: Use botulinum toxin A in the treatment of superior extremities muscle rigidity spasmodic tremor of Parkinson's disease (PD), in order to compare the clinical effect of botulinum toxin A treatment and single medicine substituted treatment.

Design: Under the random principle, use placebo-controlled method to treat four target groups: + Madopar dosage 125mg tid, Group A; 300 units of Clostridium Botulinum Toxin A (CBTX) + Madopar; Group B: 200 units of Clostridium Botulinum Toxin A + Madopar; Group C: 100 units of Clostridium Botulinum Toxin A+ electric stimulus + Madopar; Group D: placebo (sterile normal saline) + Madopar.

Subject: 40 PD patients with superior extremities muscle rigidity spasmodic tremor, 10 patients per group.

Treatment Method: 10 patients in each group were injected with toxin or placebo into their superior flexor muscles (Superior flexor muscles of 10 patients in each group were injected with toxin or placebo). For the patients of Groups A, B and C, the major determination (The determination of the main results for patients of Group A, B, & C): in the second, sixth and twelfth week before and after treatment, the podosoma status and the difficulty in handling three items by superior movement were determined. Modified Ashworth grading method was used to evaluate the muscle tension of the patients.

Result and Discussion: The results of placebo-control test proved the effect of Botulinum Toxin type A in treating superior extremities muscle rigidity spasmodic tremor.

Abstract

In treating superior extremities muscle rigidity spasm in PD, Botulinum toxin type A (LANTOX) is a pharmaceutics with great prospective. According to some non-blind tests and a placebo-control experiment, local injection of botulinum toxin A could weaken muscular tension, broaden the movement area, reduce pain and improve the hygiene of hand. To clarify the use of LANTOX and the combine use of LANTOX with other drugs in treating superior extremities muscle rigidity spasm in PD, we applied double blind and placebo-control study to do four treatments: (a) 300U LANTOX, (b) 200U LANTOXA, (c)

100U LANTOX, (d) placebo.

Method

1. Subject

The selected patients were patients of at least 6 months but less than 3 years after onset of disease classified as lower than Grade 3 by modified Hoehn-Yahr grading method. Used modified Ashworth grading method (0-5 points; 0 as no increase of muscular tension, 5 as rigidity of podosoma flexor) to test the joints of elbows, wrists and fingers of patients. It showed that there were at least included patients with superior flexor rigidity above Grade 2. Patients with obstinate spasm, treated with LANTOX before, whose limbs processed with podosoma operation, or whose medical history could not be asked due to serious albatross of cognizance, were all excluded from this study. The materials and instruments for the injection treatment of focal muscular tension limitation and muscle spasm under electromyography (EMG) guidance include: standard EMG, hollow needle coated with Teflon, surface electrode with functions of recording electrode and injection as reference, skin cleanser, disinfectant, sterile normal saline and botulinum toxin for injection.

Before the treatment, all cases or patients signed the written agreement, among those were 21 males, 19 females, average aged (47-87 years old), and average onset time was 9 months (6 -131 months). 23 were right superior muscle rigidity spasm or tremor, 7 were left superior muscle rigidity spasm or tremor, 10 were superior muscle rigidity spasm or tremor, 32 cases were mainly rigidity, 8 cases were tremor, divided equally into four groups. All clinical symptoms of the patients were by primary PD, among those 3 cases were onset before 40 years old. All patients were out-patient or in-patient, and did not withdraw throughout the whole study. Patients involved in this treatment did not take any other antispasmodic during the treatment process.

2. Design of the Study

The study process was operated under random principle, and double blind method was used for the treatment and information collection: (a) 300ULANTOX+ Madopar; (b) 200ULANTOX+ Madopar; (c) 100ULANTOX+ Madopar; (d) placebo+ Madopar. 40 patients were randomly divided into 3 treatment groups and control group, each with 10 patients.

3. Medicine Used for Treatment

LANTOX was white lyophilized powder produced by Lanzhou Institute of Biological Products, the packaging is exactly the same; 100 U of BTXA per vial, 4 ml of sterile

saline was used for reconstitution when in use.

4. Injection Method

Under EMG guidance, LANTOX (concentration of 100U/4ml) was injected into biceps muscle of arm, brachial muscle, musculus flexor carpi ulnaris, musulus flex carpi flex, deep and superficial flexor muscle of fingers, 4 – 12 injection points near the motor point of the each muscle were selected. After injection of 2.5 – 7.5U of LANTOX or placebo according to the patient's condition, temporally passive and active motion and massage were applied in each group for 3 consecutive days, once a day and half an hour for each time.

5. Evaluation of the Clinical Result

Body check for the patients at week 2, 6 and 12 before and after treatment was processed by the same judge. 1) Modified Ashworth grading method [0~5 point(s)] was used to determine the muscles of elbow, carpus and finger, in order to evaluate the muscle tension. Heohn-Yahr grading method and UPDRS were used in grading. The traditional standard 0 – 5 grading method was used for the myodynamic measurement. 2) The joints of elbow, carpus and metacarpophalangeal were checked while the body was kept in free status. For the elbow and carpus joints, the degree of flexion was the indicator in measurement by. For fingers, a 5-degree-grading method (0 as handhold, 4 as extension) was used in measurements. 3) According to the patients' self-description and the observation from nursing staffs, the degree of difficulty in handling three daily activities (washing hand, finger nail cutting and extension of the infected arm through sleeve) by patients were marked: 0 means no difficulty, 4 means unable to complete. The degree of painful from the shoulders, arms, carpus and fingers of the patients were measured by a universal painful grading standard [0 -3 point(s)].

6. Information Analysis

Use SPSS10.0, a linear equation to combine the above three independent variables, in order to evaluate the patients individually: that is $\varepsilon = x1 - (x2+x3+x4)/3$ (where "1" means before treatment, "2", "3", "4" mean the second, sixth and twelfth week respectively after treatment). The larger the total difference before and after treatment, the earlier the effect appears in the treatment, and the larger of the ε value. It was suitable in analysis of the information of treatment duration less than 12 weeks, because the duration of neuro-paralytic effect of LANTOX is more than 3 months. Use a nonparametric Kruskai-Wallis test (H test) to compare with the mean group ε value (3 independent variables complex) (using dividing value a = 0.01). If there was any

obvious total difference, Mann-whitney test (U test) would be used for pair wise comparison (using dividing value a = 0.01).

Results

1. Muscle Tension

The results of total H test showed that the P values of the obvious difference of the Ashworth test value in the comparison of the joints of elbow, carpus and finger between groups (the P values were P = 0.0012, P = 0.048 and P = 0.07). However, the decrease of muscular tension in Group A was the most obvious, especially the elbow joint, which P = 0.0001.

2. Myodynamia

The traditional standard (0 -5 level) grading method and patient self-evaluation were used to determine the myodynamia. The objective myodynamic decrease of A, B, C and D were 6/10, 2/10, 1/10 and 1/10 respectively. No sign of subjective myodynamic decrease was observed. (Not ergometer)

Muscular tremor (>50% decrease of amplitude): The amplitudes and frequencies of group A and B decreased after treatment, but no decrease in group C and D.

3. Mobility of Joints

The therapeutic effect in Group A (LANTOX+ passive and active motion and massage+ Madopar) was relatively obvious, (the comparison of the P value of the joints of carpus and finger points between groups were 0.069 and 0.058 respectively), but the differences of the ε values of the three joints in each treatment group were statistically insignificant.

4. The Degree of Difficulty in Handling Daily Activities by Upper Extremity

Among the three daily activities, only the ε values of activity A (washing hand by infected arm) showed a difference in the total distribution between the groups (P = 0.003), for the activity B (finger nail cutting) and activity C (extension of the attacked arm through sleeve), there were no obvious difference of the ε values in the total distribution between the groups, which the P value were 0.148 and 0.021 respectively. In pair wise comparison between the groups for activity A, a significant difference between Group A (300ULANTOX+ passive and active motion and massage+ Madopar) and Group C (100ULANTOX+ passive and active motion and massage+ Madopar) was shown, the P value was P = 0.0046, but there was no significant difference between Group B, C and D (placebo), P = 0.068; P = 0.078.

5. Objective Evaluation of Patients

15/20 of patients from Group A and B reported improvement, 2/20 of group C and D reported improvement. Effectiveness: 9/10 from group A, 6/10 from group B, total effectiveness rate was 53%.

6. Side Effect

All patients endured through the treatment, 1/4 reported decrease of myodynamia but there was no change in grading. There were more of them processed local turgescent bleeding, and there were 2 cases of discomposure, cardiopalmus and increase in blood pressure, no other side effect observed.

Discussion

The results of this experiment indicated that the therapeutic effect of LANTOX combined with medicine processed an obvious effect compared with dopamine treatment or placebo treatment. For the flexor muscle of PD patient, the injection dosage should be more than 300U. The muscular rigidity symptom of Group A patients, especially the elbow joints and carpus joints, were obviously improved. The ability of wearing sleeve of the infected arm was also improved.

Animal test revealed that an electric stimulus at the animal's nerve muscle joint could facilitate the absorption of LANTOX and its neuro-paralysis effect. The muscle mobility was an important factor affecting the effectiveness of neuroleprics.

A non-blind study revealed that application of muscular injection of botulinum toxin in the treatment of adult spasmodic drop foot, assisted with an electric stimulus at the injected muscle at the same time could enhance the effectiveness of the treatment.

An open study reported that only 17% (2/12) of PD of vibration amplitude (> 50% decrease of amplitude) was decreased by botulinum toxin. 5/12 cases of PD patients have a medium to obvious objective functional improvement [1]. Another study reported 35.7% of PD tremor was improved [2].

In this study, electric stimulus was not used, passive or active motion showed an obvious relief to muscle rigidity; this result consisted with the results from some open treatment studies and placebo-control tests. The patients in this study processed medium symptom level (average Ashworth marking in 2-3 points). The paralytic limbs of all patients with more than 3 points lose the normal function. During the study, the patients did not process complete hospital rehabilitation. Because the

treatment proposal was standardized, it was impossible to select the best injection points and dosage according to each patient's condition.

In conclusion, this placebo-control test indicated that, for the superior muscular rigidity of PD patients, muscular injection of botulinum toxin showed an obvious facilitation to the hygiene of hand and chopsticks handling (that is, patients could wash their hands by themselves), this method could improve the degree of comfortable and living ability of patients. However, it may have a negative effect on myodynamia.

References

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2 Pullman SL, Greene P., Fahn S. Approach to the treatment of limb disorders with botulinum toxin A. Experience with 187 Patients. *Arch Neurol*, 1996; 53(7): 617-624.