Injection of LANTOX in the Treatment of Spastic Cerebral Palsy

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Abstract

Objective: To evaluate the efficacy and side effects of local intramuscular injection of Chinese botulinum toxin type (LANTOX) in the treatment of spastic cerebral palsy.

Method: 1000 children with spastic cerebral palsy were treated with LANTOX (2.5U/kg). The therapeutic efficacy was evaluated by physician rating scale (PRS) and the improvement index of the movement and posture before and 1 month after the treatment was calculated. The tolerance to LANTOX and the side effects were also assessed.

Result: The movement and posture was improved in 99.7% children treated with LANTOX ($P<0.01$). No obvious side effects were found but weakness in injured limb in the short term after injection.

Conclusion: LANTOX proves a simple, safe and effective method in the treatment of the cerebral palsy.

Key words: Botulinum toxin type A; Cerebral palsy; Therapy

The incidence of cerebral palsy of children is 1.8% to 4% [1] in China, due to the high number of complications; the patients often have their life qualities greatly affected. Today, many physicians agreed that cerebral palsy is the largest problem worldwide as there is still no effective treatment available yet. The current treatment includes rehabilitation training, selective dorsal rhizotomy and tendon extension. However, rehabilitation therapy requires long period of training and the efficacy on older child is low; while the surgical treatments require strict indication, with the high cost and complications associated, the clinical application of surgical treatment is limited. The local injection of LANTOX is a new treatment developed in these years, it can be applied to almost every children suffered from cerebral palsy. Due to the wide indications and high efficacy, positive feedback is gained from the patients and their parents. The relatively short efficacy duration is the only drawback of the treatment, therefore repeated injection is needed. According to the 1000 cases conducted in this study, the result is summarized as follow.

Information and method

1. Clinical Information

i) Case Selection: Duration December 1999 to December 2004, 1000 patients, including 632 males and 368 females, suffered from cerebral palsy were treated in our hospital; they aged from 1.5 to 14.3 (average 6.2±3.6). In which, 170 cases (17.0%) were quadriplegic, 86 cases (8.6%) were triplegia, 482 cases (48.2%) were paraplegia, 73 cases (7.3%) were asymmetrical paraplegia, 111 cases (11.1%) were hemiplegia and the remaining 78 cases (7.8%) were monoplegia. And the palsies were not triggered by illness other than cerebral palsy.

ii) Drug: LANTOX produced by Lanzhou Institute of Biological Products were used in two preparations: 100U/vial and 50U/vial

2. Method

i) Preparation before Treatment: All cases were inpatients, and they were examined in term of their abilities in movement, standards of urine and blood, liver and kidney functions, electrocardiogram and skull CT, MRI. The improvement index of the movement and posture before treatment were assessed by PRS (physician rating scale). [2]

ii) Target Muscles Positioning: (1) Touched by hand positioning was used in 970 cases. During the injection of the sural region, assistant repeatedly help the patients to have their affected limbs dorsiflexion, therefore spasmodic muscles will be targeted by hands. (2) B-mode ultrasound guided positioning was used in 26 cases. The B-mode ultrasonic detector was placed on the proposed injection point, to visualize the target muscles (Fig. 1) (3) Electromyogram guided positioning was used in 3 cases. A tailor-made porous elctromyogram detector was used, the location of the neuromuscular junctions were detected by the end-plate noise.

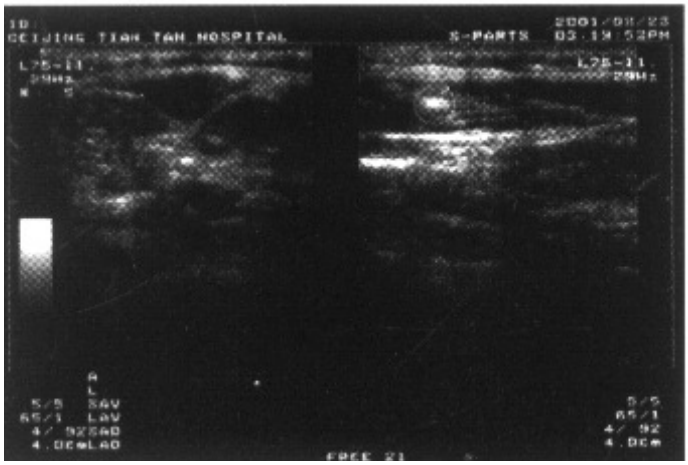

Fig. 1 Injection of LANTOX on gastrocnemius directed by B-mode ultrasound (light circle indicates the development of LANTOX)

iii) Injection Method: All patients were treated in lying position without anesthetic and tranquilizer applcation. After local disinfection, multiple-sites injections were done in each of the affected limbs with dosage 2.5 U/kg based on the weight of the patients. Each limb of patients with either both upper or both lower limbs palsied received the same dosage as the monoplegia patients; however, the total dosage did not exceed 6U/kg [3,4] in a single injection for each patient. For patients with triplegia or quadriplegic cerebral palsy, injections were done into no more than two limbs, and addition injections into the remaining limbs were done after 3 months. Adrenaline, tracheal intubation and breathing machine were prepared during the operation. Generally, patients were hospitalized after injection for observation (for at least 5 days), in which the blood pressure, breathing, pulse, heart beat rate, myodynamia, myotonia and mental status were monitored.

iv) Efficacy Evaluation: The condition of each patient was assessed by two or more pediatric neurologist or rehabilitation specialists by PRS method one month after the treatment, and the mean value of their assessments was taken into account.

v) Statistical analysis: With the help of the t-test conducted by the SPSS software, the PRS before and after the treatment were compared to work out the efficacy.

vi) Follow-up: The conditions of patients were followed 3 months and 6 months after treatment by PRS efficacy index assessment.

Result

1. After one-month postinjection, the conditions of the 1000 treated patients were improved in terms of the following PRS efficacy index: ankle position, talipes valgus or varus, genu varum or valgum, gait speed and gait. The result showed the rate of efficacy was 99.7% and the onset time was between 20 and 83 hours (average 47±23 hours). There was a significant difference between the PRS efficacy index before and after the treatment. (t-values: 3.21, 2.86, 2.73, 3.62, 3.89; $p<0.01$, also see table 1)

Table 1 Comparison of PRS before and a month after LANTOX treatment (n=1000, x±s)

Items	Ankle position	Talipes valgus or varus	Genu varum or valgum	Gait speed	Gait
Before treatment	0.66±0.82	1.22±1.02	1.44±1.00	0.72±0.98	0.64±0.65
After treatment	1.66±0.77	1.82±1.02	1.98±1.00	1.64±0.98	1.94±0.65
t	3.21	2.86	2.73	3.62	3.89
p	0.00	0.00	0.01	0.00	0.00

2. No anesthetic or tranquilizer was applied during the entire course of injection and there was no adverse reaction resulted. Apart from the temporary weaknesses in affected limbs in 5 cases, all the other cases reported no adverse reactions.

3. After 3 months postinjection, 78% of the 523 follow-up cases reported a reduction in PRS efficacy index; after 6 months postinjection, 89% of the 328 follow-up cases reported a reduction in PRS efficacy index. After half-year of treatment, majority of patients still found their gait better than before.

Discussion

Cerebral palsy is a disorder caused by non-progressive damage to the brain congenitally or within 1 month after birth. Cerebral palsy especially affecting ability to control movement and posture, and generally do not worsen over time [1]. In this study, LANTOX local injection was applied to 1000 cases, in which injection followed by hand approach, B-mode ultrasound guided approach, electromyogram guided approach were employed for the positioning of target muscles. This practice demonstrated that satisfactory results could be attained by each of these methods. The efficacy of the treatment is 99.7% using these methods. The treated patients showed significant improvements in various PRS indexes after treatment. (Table 1)

Selection of cases will exert a great impact on the treatment effectiveness; the criteria of case selection should include: palsy condition, age and IQ.

1. Palsy Condition Affects Efficacy: We found that spasmodic cerebral palsy patients with strong antagonistic muscles would have a higher efficacy under the LANTOX treatment. If the antagonistic muscles were not strong enough, the patients might even found their effected limbs even more forceless than before after the treatment. In this study, two out of the three ineffective cases were due to their

insufficiencies in antagonistic muscles strength. The remaining one is due to the combination of other diseases.

2. **Age Affects Efficacy:** The high and long-lasting efficacy and short onset time of LANTOX injection for the young sufferers aged from 1.5 to 4 was proven practically[5]. This result is related to the fact that the muscles of those young sufferers were still under the dynamic spasmodic stage instead of the fixed spasmodic stage. However, if the patients were too young, the evaluation of efficacy would be affected due to their weak muscles and immature functions in movement. In contrast, if the patients were too old, the effect of the injection will be affected due to the contracture muscles and fixed joints.

3. **Treatment Affect Efficacy:** It is easier for the well-treated patients to follow the rehabilitation instruction, because of the relief of spasm after LANTOX injection, patients will feel much better at their affected limbs. The improvement in movement and posture allowed further rehabilitation and also enhance their confidence to overcome the disease.

Promising results were shown in most cases using injection followed by hand approach to position the target muscles. However, for those over-weighted child or patients with unobvious muscle bulb, beyond depth injection occurred when followed by hand approach was employed in most of the cases. For examples, during the injection into calf muscles in the sural region, the operators injected all the solution into deep muscles - soleus, through 2 points which appear to be different in depth. If electromyogram guided positioning was used during injection, the locations of neuromuscular junctions can be positioned precisely with the aid of a tailor-made porous electrode injection needle, and therefore maximized the efficacy. The two drawbacks were: (1) Tedious disinfection process for injection needles; (2) Increase in pain level due to the blunt injection needles caused by repeated usage. Moreover, due to limited source of injection needles, the price is very high. All these factors contribute to the inconvenience in clinical application. B-mode ultrasound guided approach can correctly visualize the target muscles without creating any wound; therefore, we agreed that B-mode ultrasound guided injection is more accurate than simply injection followed by hand approach, and it gained more acceptance from the patients than EMG guided injection.

Although the onset time was different among patients [6], the efficacy in all the 1000 cases in this study basically reach optimum 1 month after the injection.

According to the follow-up result, after 3 months postinjection, 78% of the 523 follow-up cases reported a reduction in PRS efficacy index; after 6 months

postinjection, 89% of the 328 follow-up cases reported a reduction in PRS efficacy index. After half-year of treatment, majority of patients still found their gait better than before. The local LANTOX injection provided the cerebral palsy patients a basis for training as well as the rehabilitation therapy, and therefore greatly facilitate the entire treatment process. The delay in operation can also provide a sufficient time and room for the growth of affected limbs. Many parents agreed that the treatment not only did the treatment improve the movement, posture and mental conditions of their children, but also their social abilities. There were plenty clinical cases showing a complete recovery in movement after treatment. The improvement in movement can avoid the atrophy of affected limbs and thus promoting the growth of them.

In this study, apart from the 5 cases which demonstrated temporary weakness in the affected limbs after treatment, none of the cases demonstrated skin eruption, heart, lung or CNS complications. This result supported that LANTOX injection is a safe cerebral palsy treatment.

The incomplete treatment at the beginning and the regain of efficacy by follow-up injection were observed, therefore, the question of drug resistance development after repeated injections is still under investigation. Hopefully, a conclusion can be drawn in the near future.

In conclusion, it is proven by a large number of samples that LANTOX local injection is a safe, effective, simple and economical method to treat cerebral palsy.

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(Originally published in the Chinese Journal of Neuromedicine, 2005; 4(5): 488-490)