

Clinical Research of Botulinum Toxin A in the Treatment of Cerebral Palsy

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Abstract

Objective: (1) To study the efficacy of injection of botulinum toxin A combining Rehabilitative and at the same time to observe the superiority over single rehabilitation and single LANTOX focal muscular injection. (2) To investigate the economics value of home rehabilitation. (3) To explore the application of gait analysis apparatus in evaluating the efficacy after treating cerebral palsy.

Materials and methods:

-Clinical study: 162 cases with lower limb spasticity were selected and divided randomly into two groups. Group one (botulinum toxin A combining Rehabilitative): 86 cases, male 65, female 21, average 5.3 ± 3.4 years (1.8-14 years); group two (single Rehabilitative): 76 cases, male 51, female 25, average 4.7 ± 2.5 years (1.5-12 years). Rehabilitation includes OT and PT and the course is six months (five days with no treating every month). The efficacy was assessed with Physical Rating Scale before therapy, one month, three month and six month after therapy. Thirty cases were analysed with gait analysis apparatus before treatment and one month after therapy.

- Statistics methods: The data were analyzed with paired t-test and the angle of joint of knee and ankle, joint of moment were accounted with Visual 3D Version 3.0.

Results:

(1) More than 80% parents mastered the method of PT and OT and the expense of home Rehabilitation is lower than hospital Rehabilitation ($p<0.000$).

(2) There is significant difference between before therapy and one month, three months, six months after therapy in botulinum toxin A combining Rehabilitative. There is no significant difference between three months after therapy and six months after therapy in botulinum toxin A combining Rehabilitation.

(3) Pre-treatment and post-treatment result

There was no significant difference between both groups before treatment ($t=0.60$, $p=0.55$). Very significant differences were found in group one at 1 month, 3 months and 6 months after treatment ($t_1=7.78$, $p=0.000$; $t_2=9.37$, $p=0.000$; $t_3=7.18$, $p=0.000$). Botulinum toxin A combining rehabilitation was more effective than single rehabilitative since it could avoid the decreasing efficacy due to the decreasing medical effect of LANTOX.

For the trial group, PRS index improved remarkably at 1 month, 3 months and 6 months after treatment ($t_1=15.55$, $p_1=0.000$; $t_2=20.34$, $p_2=0.000$; $t_3=20.51$,

p3=0.000). For the control group, PRS index improved remarkably at 1 month, 3 months and 6 months after treatment (t1=6.98, p1=0.000; t2=6.69, p2=0.000; t3=11.72, p3=0.000). The efficacy rate was 100%.

For the trial group, PRS index at 3 and 6 months after treatment improved remarkably compared to that at 1 month after treatment (t1=3.42, p1=0.01; t2=4.07, p2=0.000). There was no significant difference in PRS index between 3 months and 6 months after treatment (t3=0.69, p3=0.49). This showed that LANTOX was most effective during the first three months in the trial group. It still showed effect from the third to sixth month. It was believed that combined therapy maintained the efficiency of LANTOX. For the control group, remarkable improvement in PRS index was found at the sixth month compared to the first and third month after treatment (t2=4.52, p=0.000; t3=2.17, p3=0.03). In group two, there was no significant difference between the first and the third month after treatment (t1=1.84, p=0.68). This showed that long term rehabilitation therapy was required for effective treatment.

Conclusion: Botulinum toxin A combining Rehabilitation is more effective than single Rehabilitative. Home Rehabilitation is cheaper than hospital Rehabilitation. It is objective and exact in analyzing the efficacy with gait analysis apparatus.

Key words: Cerebral palsy; Botulinum toxin; Rehabilitation; Ultrastructural

Introduction

The morbidity rate of cerebral palsy (CP) is 1.8-4% in China^[1]. Spasticity cerebral palsy is the most common type which is about two-third among CP. Therapy of CP is still a world-class problem. Appropriate integrated prevention measures are used to improve posture and enhance movement function so that infants' function gains the greatest improvement. Methods include medication, physiotherapy, rehabilitation training, surgical treatment, treatment of complications so that the second injury is prevented. In the past muscular tension was decreased by injection of phenol or ethanol. Since it causes pain and muscular necrosis, mostly patients do not accept the treatment. For Achilles tendon lengthening and selective dorsal rhizotomy (SDR), they have strict indications, high cost, low efficacy (50%-80%) and cause complications easily. Oral muscular relaxant such as baclofen has limited application due to its poor efficacy, apparent central sedation and other side effects.

Application of LANTOX in the treatment of cerebral palsy started in the USA in 1988^[2]. It was proved that LANTOX could relieve the pain, balance the muscular strength, improve movement functions and avoid surgery. LANTOX is thought to be an important supplementary mean in improving muscular tension and movement functions of CP patients^[3,4]. Since 1999, nationally manufactured LANTOX has been used in

large-scaled clinical research in China. The nationally manufactured LANTOX has been proved to be safe, effective, convenient and economical^[5,6].

Patients feel pain during rehabilitation therapy so they are not suitable to be cooperated with. Some patients have bone fracture and joint dislocation as the rehabilitation workers use excessive force. Many families are not able to support the medical fees as a lot of time and money is required for the rehabilitation therapy. Many patients cannot afford the expensive cost of the professional rehabilitation machines. The effect of single Botulinum toxin A injection therapy is remarkable but does not last for a long period (3-6 months). Therefore repeated injection is necessary. Repeated injection makes patients drug resistant and painful. Increasing financial burden makes patients and their families lose confidence in the therapy. The following issues are the key to this research. Rehabilitation training should be accepted by the patients and their families. Rehabilitation practitioners operate more conveniently and safe. The period of LANTOX injection should be lengthened. The age for severe spasticity surgery should be prolonged. Lowering the treatment cost can relieve the families' financial burden.

Information and Method

1) Clinical information

162 cases with lower limb spasticity were selected and divided randomly into two groups. Group one (botulinum toxin A combining Rehabilitative), 86 cases, male 65, female 21, average 5.3 ± 3.4 years (1.8-14 years); group two (single Rehabilitative): 76 cases, male 51, female 25, average 4.7 ± 2.5 years (1.5-12 years). There were 26 cases for single lower limb spasticity and 40 cases for double lower limb spasticity.

2) Experimental apparatus

- (1) Protractor
- (2) Ultrasound diagnostic apparatus – LOGIQ from US
- (3) Gait analysis test platform, including 6 infra-red video camera (Qualisys Medical AB, Sweden) and two trigger mode 3-dimensional force measurement platforms (OR6-7, AMTI, MA, USA).
- (4) Common rehabilitation instruments
- (5) Refrigerator
- (6) Electroencephalography device (K4118, Nihon Kohden)
- (7) Electrocardiogram

3) Medicine and dosage

(1) LANTOX: 50U/vial, 100U/vial, manufactured by Lanzhou Institute of Biological Products

(2) Saline water

4) Experimental methods

4.1 Rehabilitation training therapy alone

Rehabilitation training started at 48 hours after injection of LANTOX. Rehabilitation therapy included 1) Physical therapy (PT), including (1) Bobath method, (2) Rood method, (3) Vojta induction therapy; 2) Occupational therapy (OT), including (1) eating training, (2) clothing training, (3) discharging training, (4) cleaning and other daily activity trainings. The therapy lasted for 6 months. There were 25 days for therapy with 5 days break every month.

4.2 Botulinum toxin A combining Rehabilitation

4.2.1 Rehabilitation training was started at 48 hours after injection of botulinum toxin type A. Training included 1) physical therapy (PT) which included (1) Rood method, (2) Vojta induction therapy and (3) Bobath method; 2) occupational therapy which included (1) eating training, (2) clothing training, (3) discharging training, (4) cleaning and other daily activity trainings. After discharging, parents assisted the children to have rehabilitation training. Phone consultant service was provided for technical problems. Parents were welcomed to learn the techniques. Since parents were poorly-educated, they could not master the knowledge. These patients should be excluded. The training lasted for 6 months. There were 25 days for training with 5 days break every month.

4.2.2 Injection of Botulinum toxin A

(1) Preparation before injection

Electromyography and the three routine inspections were performed in all patients. Patients were also examined by CT (75%), MRI (25%), electrocardiogram (100%), electroencephalogram (100%) and evoked potentials (100%). First-aid materials and medicines (dexamethasone, adrenaline, isoprenaline, botulinum toxin type A antiserum, suction, oxygen providing machine, artificial breathing machine). Observation of muscle was guided by ultrasound. Target muscle was localized by touching (See Picutre 2). LANTOX was prepared by mixing 100 unit and 5ml saline water by slightly shaking.

(2) Injection dosage and method

Each muscle group weighed 3kg. Patients were in a prone position. No anesthesia was required. Limbs were fixed and the stretching of defected limbs was maximized. Skin

was sterilized locally. Surgeons wore disinfected gloves to touch spastic muscle, muscle bulb. Delaminated multifocal injection was performed on gastrocnemius muscle, soleus muscle, tibialis anterior and tibialis posterior. The interval between two injection sites was 3cm.

4.3 Methods of therapy evaluation

(1) Joint flexion, gait performance and velocity were measured by PRS (Physical Rating Scale). Protractor was used to measure dorsiflexion angle of knee joint and ankle joint. The unit of velocity was cm/min. 3 neurological pediatricians were required for the assessment. The measurement was taken as the average of the results. (2) Gait analysis test platform which included 6 infra-red video camera (Qualisys Medical AB, Sweden) and two trigger mode 3-dimensional force measurement platforms (OR6-7, AMTI, MA, USA) was firstly used for pre-treatment and post-treatment assessment. (30 patients in group one were selected for assessment before therapy and one month after therapy.

4.3 Reexamination

Reexamination which included PRS assessment and gait analysis was done at 1 month, 3 months and 6 months after therapy. Periodic economic of cerebral palsy treatment measured the total 6-month treatment fee of the two groups. Cost for group one included professional counselling fee, LANTOX injection fee and family self-rehabilitation fee (labour cost and self-purchase rehabilitation instruments).

4.4 Statistical analysis

Visual3D Version 3.0, an internationally used biomechanics analysis software which was organized by C-Motion Inc. was used to measure the angle of joint in the right lower limb (degree) and the moment of joint (Nm/kg). 3D coordinates and landmarks on patients' lower limbs were shown as the picture. The joint angle was zero when human was in the natural posture of standing. Normal walking cycle was known by reactive forces, heel strike (0% gait cycle), feet flat on the ground (0%-10%, gait cycle), mid-stance stage (10%-30%, gait cycle), pushoff stage (30%-60%, gait cycle), early stage (60%-70%, gait cycle), mid-swing (70%-85%, gait cycle) and swing (85%-100%, gait cycle). The data of each group was taken as the mean of data in each type. Data of the three groups were shown in the data curve graph.

4.5 Periodic economic of cerebral palsy treatment

- (1) Typical rehabilitation cost for 6 months: 10000-15000 RMB/person
- (2) Outpatient rehabilitation training cost for 6 months: $30 \times 25 \times 6 = 4500$ RMB

(3) Botulinum toxin A combining Rehabilitation cost for 6 month includes, LANTOX injection cost, rehabilitation training cost and self- rehabilitation fee (labour cost and self-purchase rehabilitation instruments).

(4) Term (2) and (3) were analysed to show the difference significance.

5) Experimental results

5.1 After 1-week training, more than 80% parents mastered the method of PT and OT.

5.2 Results of the cost required by the two methods (See the attached table)

Attached: Cost required by the two methods

Group	N	X±x	T	P
Group 1	86	4503.26±245.91	83.34	0.000
Group 2	76	1303.57±2415.54		

5.3 Statistical results of PRS value before therapy and different periods after therapy

5.3.1 There was no significant difference between both groups before treatment (t=0.60, p=0.55).

5.3.2 Very significant differences were found between the trial group and the control group at 1 month, 3 months and 6 months after treatment (t1=7.78, p=0.000; t2=9.37, p=0.000; t3=7.18, p=0.000, see Table 1).

5.3.3 For the trial group, PRS index improved remarkably at 1 month, 3 months and 6 months after treatment (t1=15.55, p1=0.000; t2=20.34, p2=0.000; t3=20.51, p3=0.000, see Table 2).

5.3.4 For the trial group, PRS index at 3 and 6 months after treatment improved remarkably compared to that at 1 month after treatment (t1=3.42, p1=0.01; t2=4.07, p2=0.000). There was no significant difference in PRS index between 3 months and 6 months after treatment (t3=0.69, p3=0.49, Table 3).

5.3.5 For the control group, PRS index improved remarkably at 1 month, 3 months and 6 months after treatment (t1=6.98, p1=0.000; t2=6.69, p2=0.000; t3=11.72, p3=0.000, Table 2).

5.3.6 For the control group, remarkable improvement in PRS index was found at the sixth month compared to the first and third month after treatment (t2=4.52, p=0.000; t3=2.17, p3=0.03) (Table 3). In group two, there was no significant difference between the first and the third month after treatment (t1=1.84, p=0.68) (Table 3). This showed that long term rehabilitation therapy was required for effective treatment.

Table 1 Comparison of PRS value between the two groups at different periods

Period	n1	Group 1 (x±s)	n2	Group 2 (x±s)	t	p
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Before therapy	86	6.78±1.55	76	6.92±1.46	0.60	0.55
1 month after therapy	84	8.82±1.39	76	6.92±1.46	7.78	0.00
3 months after therapy	83	11.42±1.25	71	9.27±1.59	9.37	0.00
6 months after therapy	83	11.46±1.30	65	9.74±1.18	7.18	0.00

Table 2 Comparison of PRS index between the two groups at different periods before and after therapy

Group	Before therapy	1 month after therapy	3 months after therapy	6 months after therapy	t1	t2	t3	P1	P2	P3
		(x±s)	(x±s)	(x±s)						
1	6.88±1.61	10.68±1.57	11.43±1.26	11.55±1.24	15.55	20.34	20.51	0.00	0.00	0.00
2	6.84±1.46	8.59±1.63	8.74±1.99	9.79±1.60	6.98	6.69	11.72	0.00	0.00	0.00

Note: t1, comparison between before therapy and 1 month after therapy; t2, comparison between before therapy and 3 month after therapy; t3, comparison between before therapy and 6 month after therapy. P1, comparison between before therapy and 1 month after therapy; P2, comparison between before therapy and 3 month after therapy; P3, comparison between before therapy and 6 month after therapy.

Table 3 Comparison of PRS index between the two groups at different periods after therapy

Group	1 month after therapy	3 months after therapy	6 months after therapy	t1	t2	t3	P1	P2	P3
	(x±s)	(x±s)	(x±s)						
1	10.68±1.57	11.43±1.26	11.55±1.24	3.42	4.07	0.69	0.01	0.00	0.49
2	8.59±1.63	8.74±1.99	9.79±1.60	1.84	4.52	2.17	0.68	0.00	0.03

Note: t1, comparison between before therapy and 1 month after therapy; t2, comparison between before therapy and 3 month after therapy; t3, comparison between before therapy and 6 month after therapy. P1, comparison between before therapy and 1 month after therapy; P2, comparison between before therapy and 3 month after therapy; P3, comparison between before therapy and 6 month after therapy.

5.3.7 Analytical results of the angle of knee joint and ankle joint and walking velocity by gait analysis

Table 4 Gait analysis in comparison of change of the angle of knee joint

Group	n	X±s	F	p
Control	30	10.3909±10.3909		0.00*
Before therapy	30	6.9070±6.9070	47.6	0.00#
After therapy	30	15.4759±15.4759		0.00•

Note: *Comparison between the control and before therapy; # Comparison between the control and after therapy; •Comparison between before and after therapy

Table 5 Gait analysis in comparison of change of the angle of ankle joint

Group	n	X±s	F	p
Control	30	.8963±4.39603		0.74*
Before therapy	30	.6173±3.09056	47.6	0.00#
After therapy	30	5.7101±1.77211		0.00•

Note: *Comparison between the control and before therapy; # Comparison between the control and after therapy; •Comparison between before and after therapy

Table 6 Gait analysis in comparison of the change of walking velocity

Group	n	X±s	F	p
Control		157.70±21.65		0.44*
Before therapy		154.25±15.21	39.24	0.00#
After therapy		122.00±13.76		0.00•

Note: *Comparison between the control and before therapy; # Comparison between the control and after therapy; •Comparison between before and after therapy

6) Discussion

For the past 10 years, LANTOX were widely used in treatment of spasticity cerebral palsy and dystonia diseases^[7]. Practical application showed its effectiveness^[8]. After treatment, muscular strength decreases and degree of joint motion, gait performance and length of muscle tissue increases. The strength of antagonist muscles improved as well. LANTOX comes into effect at 12-72 hours after injection^[5, 9]. Generally dramatic effect is shown at the first week^[10]. In the treatment of lower limb spasm, injection at gastrocnemius and soleus improves movement of ankle joint, foot inversion and knee inversion remarkably^[5, 11]. Electrophysiology proves that compound motor action potential starts to decrease at 48 hours after injection of LANTOX. The decreasing trend peaks at week 1 to week 3. The drug fluctuates most from third week to sixth month^[5, 10]. It is found that disorder appears in the improved function again at 3-6 months after therapy. Spasticity is shown in relieved muscles. The reason is explained as follows. Nerve ending still comes into contact with the muscle after injection of LANTOX.

Motor axon does not disappear yet. This maybe because muscles release some growth factors and motor end-plate enlarges. Sprouting occurs at the end-plate, axon end and the neighboring Ranvier's node. Both the number of motor end-plates on a single muscle tissue and tissues controlled by a single motor nerve axon increases. One muscle tissue can be controlled by a few motor nerve axons. Sprouting starts the 28th day after injection. It takes 90 days to restore functional relationship between nerve muscles^[12]. For more serious matter, it causes muscular spasm. The sprouting is consistent to the clinical trial. Repeated injection is necessary^[13]. Both repeated injection within short period and increasing dosage cause the production of antibodies^[14].

As mentioned above, both rehabilitation training and single LANTOX injection have their disadvantages and influencing factors. This research tried to solve the following two problems. These include feasibility and continuity of treatment in cerebral palsy and superiority of botulinum toxin A combining rehabilitation.

1) The easibility and continuity of rehabilitation treatment in cerebral palsy was paid much attention. When the patients were in hospital, their parents were provided rehabilitation technical training. This made them know the importance of formal rehabilitation therapy so that their motivation was raised. Once they grasped the knowledge of rehabilitation technical skills, treatment in cerebral palsy became possible in the means of time, place and money. It was proved that rehabilitation training became easier after injection of LANTOX. Parents mastered the method of PT and OT after one week training. They could undergo the training at home after that. Theoretically, it was more effective for children to have training at home since they are more familiar to the environment. There was a remarkably significant difference between the fee for rehabilitation training at home and expense of professional rehabilitation training ($p < 0.000$).

2) The efficiency of botulinum toxin A combining rehabilitation was more remarkable than that of single rehabilitative. The short lasting effect of single LANTOX injection was also overcome. Very significant differences were found between the trial group and the control group at 1 month, 3 months and 6 months after treatment ($t_1=7.78$, $p=0.000$; $t_2=9.37$, $p=0.000$; $t_3=7.18$, $p=0.000$). It showed that LANTOX combining rehabilitation was more effective than single rehabilitative. Local injection was convenient and the muscle was localized by means of functional anatomy, touching, ultrasound and electromyography. The abnormality in the function and structure of cerebral palsy could be resolved. Here are some examples. Injection at iliopsoas and musculus quadriceps femoris can relieve the deformity in cross-flexor. Injection at

biceps femoris can relieve genuflex deformity. Injection at thigh muscle can relieve scissor gait. Injection at gastrocnemius and soleus can relieve talipes equines. Injection at tibialis anterior can relieve talipes equinovarus. Injection at peroneus longus and peroneus brevis is helping in correction of horseshoe foot eversion. This flexible method was effective in the treatment. .

After injection of LANTOX, the spasticity was relieved and spastic muscle issue was elongated so that the degree of joint movement increased. These helped in the recovery of complex deformity and improvement of posture. Increasing awareness of patients and their parents to be actively involved made rehabilitation training more easily to be operated. More resources were spent on research to have a better therapeutic result. Research showed that there was a significant difference between the trial group and the control group at 1 month, 3 month and 6 month after treatment. It was expected that this method was more effective than single rehabilitative in the long term.

For the trial group, PRS index improved remarkably at 1 month, 3 months and 6 months after treatment ($t_1=15.55$, $p_1=0.000$; $t_2=20.34$, $p_2=0.000$; $t_3=20.51$, $p_3=0.000$). For the trial group, PRS index at 3 and 6 months after treatment improved remarkably compared to that at 1 month after treatment ($t_1=3.42$, $p_1=0.01$; $t_2=4.07$, $p_2=0.000$). There was no significant difference in PRS index between 3 months and 6 months after treatment ($t_3=0.69$, $p_3=0.49$). The most effective time of combined rehabilitative was the first three months after injection. The third month was the peak time of its maximum effectiveness. Past clinical found that spasticity in limbs occurred again at 3 months after injection. In this research, LANTOX still came into effect at 6 months after therapy. This prevented the decreasing effect due to the decreasing effect of LANTOX. This could delay the time for repeated injection and surgery of severe spasticity.

For the control group, PRS index improved remarkably at 1 month, 3 months and 6 months after treatment ($t_1=6.98$, $p_1=0.000$; $t_2=6.69$, $p_2=0.000$; $t_3=11.72$, $p_3=0.000$). The effect of rehabilitative was most remarkable at the first month after treatment. There was no significant difference between the first and the third month after treatment ($t_1=1.84$, $p=0.68$). Remarkable improvement in PRS index was found at the sixth month compared to the first and third month after treatment ($t_2=4.52$, $p=0.000$; $t_3=2.17$, $p_3=0.03$). Factors like muscular spasm determined the time of rehabilitation therapy.

LANTOX is manufactured by the Lanzhou Institute of Biological Products. Clinical trial in 2500 cases shows that the result is reliable with few undesirable effects and low cost.

Relief of muscular spasm has the following benefits. 1) The balance between synergist and antagonist muscles was restored. Patients felt less painful during movement. This increased active movement. 2) Less pain made children become cooperative during rehabilitation training. This lessened the doctors' physical burden. 3) Balance in muscular strength improved joint structures and facilitated normal bone development. 4) Relief in synergist muscle made movement of antagonist muscle possible. This helped rehabilitation training to be carried out easily. 5) As both active and passive movement improved, patients' initiative in the rehabilitative increased. The coordination of the high central nervous system was enhanced. This helped the elongation of effective time of LANTOX^[15].

The curative effects after injection of LANTOX has been studied recently. It has been found that small age, hemiplegia, light damage in motor nerve unit, walking with support, high intelligence, good eyesight were the factors to results in good curative effects^[16]. Sharan Deepak thinks that patients younger than 4 years old without muscular spasm show best response to the injection of LANTOX^[17].

There are few studies about gait analysis in curative effects of cerebral palsy. In this study, gait analysis test platform, including 6 infra-red video camera (Qualisys Medical AB, Sweden) and two trigger mode 3-dimensional force measurement platforms (OR6-7, AMTI, MA, USA) was used.

Initial results of curative effect in the treatment were obtained. The shortcomings were inconvenient use of the apparatus, high cost and difficult approach to patients with difficulty in movement.

7) Conclusion

Botulinum toxin A combining Rehabilitation is more effective than single Rehabilitative. Home Rehabilitation is cheaper than hospital Rehabilitation. It is objective and exact in analyzing the efficacy with gait analysis apparatus.

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