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Efficacy analysis of ultrasound-guided local injection of botulinum toxin type A treatment with orthopedic joint brace in patients with cervical dystonia

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Abstract. – OBJECTIVE: To study the efficacy of ultrasound-guided local injection of botulinum toxin type A (BTX-A) treatment with orthopedic joint brace in patients with cervical dystonia (CD).

PATIENTS AND METHODS: A total of 105 patients with cervical dystonia were selected and randomly divided into medication treatment group (A group), botulinum toxin treatment group under the guidance of ultrasound treatment (B group) and botulinum toxin under the guidance of ultrasound treatment combined with orthopedic joint brace treatment group (C group). Tsui scale and Spitzer quality of life index was applied to evaluate the spasm and quality of life. The scores of Tsui scale and Spitzer quality of life index were compared after ultrasound-guided local treatment for one month, three months and six months.

RESULTS: The difference in Tsui and Spitzer scores before and after the treatment of oral medications were not statistically significant ($p > 0.05$). Whereas, the differences in Tsui and Spitzer scores before and after the treatment between local injection of BTX-A treatment group and orthopedic joint brace combined with BTX-A injection group were statistically significant ($p < 0.05$). Also, the difference in Tsui and Spitzer scores of orthopedic joint brace combined with BTX-A injection group at 3 months, and 6 months were statistically significant compared to local injection of BTX-A treatment group ($p < 0.05$).

CONCLUSIONS: Ultrasound-guided local injection of BTX-A combined with orthopedic brace could significantly reduce muscle tension and improve quality of life.

Key Words:
Color Doppler ultrasound, Botulinum toxin type A, Cervical dystonia, Orthopedic brace.

Introduction

Cervical dystonia (CD) is the most common adult-onset focal dystonia, characterized by repeated involuntary contractions of neck muscle, which causes cervical muscle spasm, pain and abnormal head position, seriously affecting the normal life of patients[1-2]. The efficacy of oral medication is poor and the side effects are many. Botulinum toxin Type A (BTX-A) has been an effective drug widely used for the treatment of dystonia diseases since late 1980s[3-6]. The discussion on the influence of combined treatment of color ultrasound guided local injection of BTX-A with orthopedic joint brace for CD have important clinical implications.

Patients and Methods

Patients

The data were derived from 105 cases of CD patients hospitalized and outpatients of our hospital from January 2007 to January 2011, included 62 males and 43 females, aged 22-57 years, and the course of disease was 6 months to 10 years. Patients who had general muscle weakness such as secondary dystonia, myasthenia gravis, Eaton-Lambert syndrome, motor neuron disease and, those who suffered from allergies, pregnant women, and those had severe vital organ dysfunction, such as heart dysfunction, liver dysfunction, kidney dysfunction, those who had severe cognitive disorders, mental disorders, history of asthma awareness, fever, infections as well as those who had taken drugs aggravating the transmission dysfunction on neurological-muscular joint within a

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week were excluded. This test was approved by the Ethics Committee of the hospital. Entire test lasted for a period of 15 months. The above-mentioned patients were registered in the groups after signing informed consents. All patients went through complete check-up, including blood routine examination, urine routine examination, liver and kidney function examinations, electrocardiogram, electroencephalogram and other examinations before receiving treatment.

The selected patients were randomly divided into medication treatment group (group A), botulinum toxin injection treatment group (group B) and combined treatment of ultrasound-guided botulinum toxin injection and orthopedic joint brace group (group C). The differences in scores for sex, age, muscle spasticity, and daily life index among three groups were not statistically significant ($p > 0.05$).

Clinical classification and reference site as well as dose of injection for major muscles are illustrated in Table I.

Methods

Medication

Oral drugs such as trihexyphenidyl, diazepam, haloperidol, baclofen, carbamazepine and other drugs were selected depending on the condition of patients and the patients took those drugs for six months.

BTX-A Injection

BTX-A injection was produced by the Lanzhou Institute of Biological Products of Ministry of Health. It was lyophilized to a crystallizing agent, with a content of 100U in each ampoule. Injections were given while patients were either sitting or lying down. The preparation of normal saline was 25 u/mL. After preparation, it should be injected within 1h as much as possible (the longest time should be ≤ 4h). Skin test syringe of 1 mL, with needle of 4.5 mm or 5 mm (with needle of 6 mm for deep muscle injection) was used and 5 u of BTX-A on each site was injected. The injection site and injection dose were determined by two chief physicians of the Department of Neurology, who were not aware of the test design according to muscle size, number, CD type, and spasticity. To apply stratified multi-point injection method, and injection to the blood vessels was forbidden. The distance between two sites was 2 to 4 cm. The patients with poor efficacy were injected once again a week later. During the follow-up period of medication and injection treatment, Tsui Scale score was evaluated for one month, three months, and six months respectively to assess the degree of neck spasms in patients. Spitzer Quality of Life Index score was evaluated to assess quality of life of patients, independently conducted by two physical therapists unaware of the experimental design and according to unified form; results were taken as the mean of two values. The assessment results, onset time, the peak efficacy time, the period efficacy lased, side effects, adverse reactions and inspection results of urine routine examination, liver and kidney function, electrocardiogram and electroencephalogram before and after the treatment were recorded in detail by a chief physician unknown to the test design.

Table I. Reference site and dose of injection for muscle.

Type	Number of cases			Muscle	Number of sites	Dose
	A	B	C			
Rotational torticollis	18	18	18	Thoracic paraspinal muscle (contralateral)	10	50u
				splenius capitis muscle (ipsilateral)	6	30u
Laterocollis	7	9	9	Thoracic paraspinal muscle (contralateral)	10	50u
				splenius capitis muscle (ipsilateral)	6	30u
				trapezius muscle (ipsilateral)	10	50u
Retrocollis	5	5	6	Splenius capitis muscle (bilateral)	10	50u
				trapezius muscle (bilateral)	10	50u
				musculus levator scapulae (bilateral)	10	50u
Mixed	3	4	3	Thoracic paraspinal muscle (bilateral)	10	50u
				splenius capitis muscle (bilateral)	10	50u
				trapezius muscle (bilateral)	10	50u

Ultrasound-Guided Injections Used a Portable Ultrasound Machine

The operation steps were: (1) position: the patient lied or prostrated themselves with their necks exposed; (2) the site to be injected was disinfected using iodine routinely. An appropriate amount of coupling agent was smeared with the probe of ultrasound instrument after the skin was dry; (3) approximately 50 ml of normal saline was extracted with a syringe, and injected into the water capsule, the water capsule was placed between the probe and the skin, and improved ultrasound image definition; (4) under the guidance of ultrasound location map, clear and definite the muscle to be injected into and its cross-sectional area, and the injection site and dose is determined; (5) the needle was inserted next to the probe, and the BTX-A was accurately injected into selected muscles under the ultrasound direct viewing, stratified (two or three) according to the thickness of the muscle and carefully avoiding blood vessels and nerves.

Orthopedic Brace

Patients used external fixator, produced by Xiangyang Yue Fei Recovery Equipment of Prosthetics and Orthotics Co., Ltd., for head, neck, chest, and back for 6-8 hours a day. Patients were frequently checked to avoid compression injuries resulting from orthotics.

Evaluation Standard

Muscle Spasticity Score

According to Tsui scale classification[7] and score were graded in terms of the aspects such as (1) degree of torticollis, (2) time of head tilt, (3) lift of shoulders, (4) tremor or convulsion of head respectively, the aggregate score; (1)* (2) + (3) + (4), and total score was 25 points.

Quality of Life Index Score

According to Spitzer Quality of Life Index Scale[8], score in terms of the aspects such as (1) capacity for action, (2) daily life, (3) healthy feeling, (4) support from family and friends, (5) understanding of entire life respectively. The total score was 10 points.

Statistical Analysis

SPSS13.0 statistical software (SPSS Inc., Chicago, IL, USA) was applied to process data. Measurement of data are represented by ($\bar{x} \pm s$), and $\bar{x}$ test was applied for the comparisons between different treatment groups and between pre-treatment and post-treatment. $p < 0.05$ was considered statistically significant.

Results

There were no significant differences for Tsui, and Spitzer quality of life index scores before and after oral medication treatment (see Table II).

Significant differences were observed for Tsui, and Spitzer quality of life index scores before and after local injection of BTX-A treatment and local injection of BTX-A treatment with orthopedic joint brace ($p < 0.01$) (see Table II).

Statistically significant differences were detected for Tsui, Spitzer quality of life index scores at three months and six months between BTX-A treatment and BTX-A treatment with orthopedic joint brace groups (Table II).

Discussion

At present, not enough is known about the mechanism of CD[9-12]. Clinically the treatment is symptomatic, making the symptoms remit, to improve the quality of life of patients and prevent

Table II. Comparison of Tsui, and Spitzer Quality of Life Index Scores before and after treatment among Group A, Group B and Group C.

	Before treatment		After 1 month of treatment		After 3 months of treatment		After 6 months of treatment	
	Tsui	Spitzer	Tsui	Spitzer	Tsui	Spitzer	Tsui	Spitzer
A	19.4 ± 2.5	3.2 ± 1.5	18.9 ± 2.6	2.8 ± 2.1	18.8 ± 2.1	2.7 ± 2.7	18.6 ± 2.0	2.6 ± 1.8
B	18.6 ± 3.1	2.9 ± 1.8	10.2 ± 3.6$^{\Delta}$	4.4 ± 2.1$^{\Delta}$	8.6 ± 3.4$^{\Delta}$	5.2 ± 1.4$^{\Delta}$	5.3 ± 3.9$^{\Delta}$	7.1 ± 2.2$^{\Delta}$
C	19.1 ± 4.1	2.8 ± 2.1	9.2 ± 3.9$^{\Delta}$	3.7 ± 2.7	5.8 ± 3.7$^{\Delta,\#}$	6.4 ± 2.2$^{\Delta,\#}$	3.2 ± 2.3$^{\Delta,\#}$	8.3 ± 1.7$^{\Delta,\#}$

$^{\Delta}$Means the comparison with pre-treatment $p < 0.01$; $^{\#}$Means the comparison with group B $p < 0.01$.

complications from happening. Oral medication is effective for some patients with CD to some extent, the duration of efficacy is short, and the side effects such as vertigo, sleepiness, weakness and so on occurred frequently[13]. The results of this study testified that the score comparison ($p > 0.05$) of group A after treatment for one month, three months and six months was relatively low. The treatment results of partial closure of acupuncture therapy and other treatments are not satisfactory, and the disease relapses in the short term[14]; the trauma of selective resection for spastic muscle is large and easy to relapse, and is not used as much[15].

BTX-A has been used to treat a variety of dystonia diseases; BTX-A treatment has become the first choice in many countries for CD[16], and a number of authors at home and abroad have proven that it is a safe and effective treatment[17,18,] and it can significantly improve quality of life of patients[19]. The experimental results showed that: local injection of BTX-A was effective, consistent with relevant reports, and indicated that combination therapy could improve efficacy ($p < 0.05$). The mechanism of ultrasound-guided local injection of botulinum toxin type A (BTX-A) treatment with orthopedic joint brace may include the following: (1) mainly through splitting the 25kD synaptosome-associated protein on the internal face of presynaptic membrane of neuromuscular junction, to inhibit release of acetylcholine and the activity of muscle spindle, relaxes muscles, relieves muscles with spasms CD, and remits the symptoms; (2) BTX-A also inhibits the release of receptors for pain and hurts substance P and reduces the pain due to long-term tension, contraction, spasm of muscle of patients with CD, thus, improving patients' comfort, and significantly reducing mental disorders and mental stress of patients with CD, so that the spirit and the neuromuscular system of the patients can be re-established in good coordination, resulting in improved quality of life of patients; (3) botulinum toxin can give rise to the reconstruction of the central nervous system through the sensory system (sensory track) except through transmission path[20]; (4) orthotics can reduce the damage to the vestibular function resulted from long-term abnormal posture; studies have reported that the occurrence of CD is related to the damage of the vestibular system[21]; for example, CD patients may have dizziness, vertigo, nystagmus, ataxia, etc. Using orthotics and BTXA together can better stretch muscles, adjust and prevent contractures, and enhance the function to the maximum[22]. At the same time it can amend abnormal posture caused by the reduction of muscle tension, and the increase of coordinated muscle tension after injection[23].

As a new technology for intramuscular injection positioning, ultrasonic is free from trauma, pain, and with high resolution. The nerve blood vessels of target muscles and its surroundings can be displayed clearly. Under ultrasonic, the muscles showed hypo echo, tendons showed tubular hyperechoic line (fibrous), and muscle fascia was characterized by hypo echo. The resolution of high frequency ultrasound is sharp; nerve blood vessels of target muscles and its surroundings are clear and visible[24,25]; water capsule can reduce the influence of probe on the needle-point, can fix the position of the needle and site, and improve the resolution of ultrasonic image at the same time. It is easy to make water capsules, and these can be clinically applied widely. In this paper, the color Doppler ultrasound instrument utilized could fully meet the requirements of positioning. Under the guidance of this device, the operator can not only accurately locate the way for positioning inserting needle but can also reach the target muscle, and avoid surrounding blood vessels and nerves. This technique is strongly operable, safe and effective and worth to be popularized.

Support of ultrasound-guidance helps reduce botulinum toxin injection amount without affecting the efficacy and ensure that the medicine accurately reaches to the site of action with a lower occurrence rate of adverse reactions. The results of the present study showed no serious side effects, allergic reactions, swallowing disorders, drinking cough, which was related to the dose of drug and method used. However, the prevalence rate of adverse reactions on related reports was 12%-80%[26].

Conclusions

Clinicians should be fully aware of clinical features, diagnosis and treatment of dystonia, carefully observe and record a variety of incentives of symptom remission and exacerbation, follow the principle of individuality, focus on symptomatic treatment, and use comprehensive treatment such as drugs, psychological treatment, rehabilitation, surgery and other ways to improve efficacy, and the quality of life of patients.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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