Treatment of Cervicogenic Headache with Botulinum Toxin A: a Double-Blind Trial

Zhang Zongfeng, Yao Meng, Zhang Yi

(Treatment Center of Cervicolumbodynia, the Second Affiliated Hospital of Harbin Medical University, Haerbin 150086, Heilongjiang, China)

Abstract

Objective: To determine whether therapy with botulinum toxin A may prove to be an effective treatment for headaches of musculo-skeletal origin.

Method: According to double-blind principle, 40 patients suffering from cervicogenic headache were divided into the treatment group and the control group. Each member of the treatment group received liquor diluting botulinum toxin A (50 units/ml), while each member of the control group received a placebo dose consisting only of saline.

Result: At both 2 and 4 weeks post injection, the treatment group showed a statistically significant reduction in: (1) the number of headache days per months (2.0 ± 2.4, 2.2 ± 2.6) and (2) the headache index (2.5 ± 3.5, 3.5 ± 3.6), as compared with either the control group (14.6 ± 5.2, 16.1 ± 5.2 and 24.2 ± 14.1, 26.3 ± 11.2) ($P < 0.01$) or the pre-injection treatment group (14.7 ± 5.8 and 32.6 ± 19.6) ($P < 0.01$).

Conclusion: The injection of botulinum toxin A into myofacial trigger points is an effective treatment for headaches of musculo-skeletal origin.

Key words: headache/therapy; double-blind method; botulinum toxin type A/therapeutic use

Introduction

Cervicogenic headache is a syndrome caused by the structural lesion of upper cervical nerve (C_{1-3}) and its predominant nerve. Its clinical manifestations are mainly chronic and unilateral headache. It is a kind of referred pain [1]. Nowadays, therapies using are mainly target to the lesion of upper cervical nerve and its predominant joints, intervertebral discs, dura maters and blood vessels [2-3].

However, there is still no cervicogenic headache therapy which is targeting on the lesion of cervical muscle. A research [4] shown that botulinum toxin A could be an effective therapy for cervicogenic headache with musculo-skeletal origin. This research further proved the efficacy of botulinum toxin A in the treatment of cervicogenic headache with musculo-skeletal origin and developed new therapy for cervicogenic headache.

Material and Method

1. Material

40 out-patients of our hospital were selected during January 2001 to June 2002. There were 18 male patients and 22 female patients, aged from 24 to 59 (mean 42 years old).

Selection criteria: Match the diagnostic criteria of the cervicogenic headache established by the International Headache Society [5], and the following requirements. (1) Course of cervicogenic headache is not less than 6 months; (2) Do not receive any medicine treatment within 3 months recently (including contraceptive drugs); (3) Regressive change of the cervical vertebrae is showed in the X-ray. All patients were suffered from headache. Among the patients, 26 patients showed obvious frontal and temporal pain and 22 patients showed occipital pain. Localized pain and headache could be triggered or be aggravated by pressing the trigger points at the temporal, (upper) trapezius, splenius capitis and (upper) sternocleidomastoid muscle.

Elimination criteria: (1) Patients with other pain diseases; (2) Patients with tumor at the neck, or fracture or dislocation of bone were eliminated by imaging; (3) Patients with neurological or other systematic disease.

2. Methods

Patients were randomly divided into treatment group and control group according to the double-blind principle. Botulinum toxin A and placebo (normal saline) were injected into the trigger points at temporal, (upper) trapezius, slenius capitis and (upper) sternocleidomastoid muscle of the treatment group and the control group respectively. Botulinum Toxin Type A for Injection (LANTOX), which is a lyophilized crystalline powder, was produced by Lanzhou Institute of Biological Products with license number: (97) Drug Approval License (Lan) S-01. Each vial of Botulinum Toxin Type A for Injection contains 100 U. It was reconstituted by 2.0 ml normal saline (produced by the Second Affiliated Hospital of Harbin Medical University). 0.1 ml of Botulinum Toxin Type A for Injection was injected per trigger point. Multiple sites were injected with total dosage not more than 100 U. 0.1 ml of normal saline was injected per trigger point. Multiple sites were injected with total dosage not more than 2.0 ml.

3. Statistical Analysis

SAS software was applied to carry out *t*-test to compare data between treatment group

and control group, and data before and after the treatment.

Result

1. Headache Assessment

Headache severity was classified into four grades by the impact of headache on the patients' daily life and work: Grade 0 – no headache; Grade I (mild headache) – mild headache, no impact in daily life and work; Grade II (moderate headache) – relatively acute headache, affecting the daily life and work; Grade III (severe headache) – severe headache, cannot maintain the daily life and work, patients even need to stay in bed. The number of headache days per month is the number of days suffered from headache within one month. Headache index is the multiple of number of headache days per month and headache severity. According to Tfelt-Hansen *et al* [6], the number of headache days per month and the headache index are recommended in the headache treatment assessment.

2. Treatment Result

3 patients were dropped out by personal reasons respectively. See Table 1.

Table 1 Number of headache days per month and headache index before and after treatment in both groups ($\overline{\chi} \pm s$)

Groups	n	Before treatment	
		Number of headache days per month	Headache index
Groups of botulinum toxin A	19	14.7 ± 5.8	32.6 ± 19.6
Groups with saline	18	16.3 ± 5.3	31.2 ± 13.1
Groups	**n**	**Two weeks after treatment**	
		Number of headache days per month	**Headache index**
Groups of botulinum toxin A	19	2.0 ± 2.4[ab]	2.5 ± 3.5[ab]
Groups with saline	18	14.6 ± 5.23	24.2 ±14.1
Groups	**n**	**Four weeks after treatment**	
		Number of headache days per month	**Headache index**
Groups of botulinum toxin A	19	2.2 ± 2.6[ab]	3.5 ± 3.6[ab]
Groups with saline	18	16.1 ± 5.21	26.3 ± 11.2

Note: Compared with that before the treatment [a]$P < 0.01$, compared with the group of saline [b]$P < 0.01$.

Discussion

1. Relationship Between Trigger Point and Cervicogenic Headache

Trigger point is a touchable point at the skeletal muscle fibre with high limitation and easy irritation in the tonicity. Simons *et al* [7] found that there is a spontaneous and

continuous low frequency electrical potential (10 ~ 50 μV) at the motor end plate of the trigger point. It is different to the action potential, which is high and acute (100 ~ 600 μV), and is called End-plate Noise. End-plate Noise may induce the release of acetylcholine at the synapse between nerve and muscle and trigger the post-synaptic membrane potential. These actions may induce calcium ions from sarcoplasmic reticulum and extra cellular entering to the cytoplasm through cell membrane. It may lead to continually shrinkage of muscle fibre and increase the consumption of local oxygen and high-energy phosphate. Continually shrinkage of muscle fibre may damage the local micro-circulation and reduce supply of oxygen and energy, too. Therefore, vicious cycle may be formed. It leads to the accumulation of acidic metabolites and cause the crisis of energetic metabolism. Crisis in energy metabolism may damage the tissue directly and induce the release of cytokine, such as 5-hydroxytryptamine, histamine and kassinin kinin. Both cytokine and acidic metabolites are the algogenic substance of the neurological system. These substances may induce afferent impulse of pain sensation. An important characteristic of myofacial trigger point is the referred pain caused by the mechanical stimulation. Some researches showed that this pain is closely correlated to central integration. When myofacial trigger point was pressed and the pain output signals were generated at the receptive field, these signals would undergo convergence and facilitation in the central nervous system. Then, those signals would excite the related sensory neurons and generate the referred pain. Temporal, (upper) trapezius, splenius capitis and (upper) sternocleidomastoid muscle are predominated by the upper cervical nerve. Pains generated at the myofacial muscle are transmitted to central nervous system through the upper cervical nerve. Some research showed that the sub-nucleus of the caudal part of nucleus tractus spinalis nervi trigemini, which connected with the trigeminal nerve, could be found at the C_{1-2} segment of the cervical spinal. Moreover, its caudal part could be found at the C_3 segment of the cervical spinal and connected with posterior grey matter of the upper cervical spinal (C_{1-3}, same as below). Therefore, Biondi [8] thought that afferent algesthesia, from the upper cervical nerve, could be converged and facilitated in the anatomical structures and trigeminal nerve aforementioned. Then, it would induce the referred pain in head.

2. Pharmacological Action of Botulinum Toxin A and its Significance in the Cervicogenic Headache Treatment

Botulinum toxin A is a pre-synaptic neurotoxin produced by *Clostridium botulinum*. It could block the influx of calcium ions and inhibit the acetylcholine release from the nerve terminal; and then relieve the muscle fibre which is contracted continually [9].

In this clinical experiment, botulinum toxin A was injected into the trigger points of (upper) trapezius, splenius capitis and (upper) sternocleidomastoid muscle. It could eliminate the continually contraction of muscle fibre induced by the end-plate noise. Thus, it could alleviate algesthesia of the posterior branch of upper cervical nerve caused by the acidic metabolite and cytokine. There are significant different in the number of headache days per month and the headache index of 2 and 4 weeks after the treatment compared with the control group and that before the treatment ($P < 0.01$). Accordingly, it is believed that myofacial trigger point have an important role in the initial phase of the cervicogenic headache mechanism. And, it is proved that botulinum toxin A injection in the trigger points is an effective method for treating cervicogenic headache.

3. Deficiency

In this research, no alleviation or non-complete alleviation were found in some patients after the botulinum toxin A injection in the trigger points. It suggested that there should be some other unknown factors which may induce the cervicogenic headache; thus some patients should be treated by a combined treatment including the botulinum toxin A injection at the trigger points. Moreover, there is no significant difference in the number of headache days per month and headache index in between 2 weeks and 4 weeks after the treatment ($P > 0.05$); however, the actual value was in an increasing tendency. This may be due to the sprout of nerve and resumption of its predomination to muscles. This mechanism may affect the long-term effect of the botulinum toxin A in the cervicogenic headache treatment.

References

1. Bogduk N. Cervicogenic headache: anatomic basis and pathophysiologic mechanisms. *Curr Pain Headache Rep*, 2001; 5(4): 382-386
2. Silverman SB. Cervicogenic headache: interventional, anesthetic, and ablative treatment. *Curr Pain Headache Rep*, 2002; 6(4): 308-314
3. Pan GY, Lu W. Investigations of three ways of curing cervical headache of children. *Chin J clin Rehabil*, 2002; 6(16): 2422.
4. Evers S, Rahmann A, Vollmer HJ, *et al*. Treatment of headache with botulinum toxin A-a review according to evidence-based medicine criteria. *Cephalalgia*, 2002; 22(9): 699-710.
5. Sjaastad O, Fredrilsen TA, Pfaffenrath V. Cervicogenic headache: diagnostic criteria. *The Cervicogenic Headache*, 1998; 38(6): 4425
6. Tfelt-Hansen P, Olesen J. Methodological aspects of drug trials in migraine. *Neuroepidemidogy*, 1985; 4(4): 204-226
7. Simons DG, Hong CZ, Simons LS. Endplate potentials are common to midfiber myofacial trigger

points. *Am J Phys Med Rehabil*, 2002; 81(3): 212-222

8. Biondi DM. Cervicogenic headache: mechanisms, evaluation, and treatment strategies. *J Am Osteopath Assoc,* 2000; 100(9): 7-14
9. Sun XM, WU XL, Zhao SS, Zhang QY, Bao SR. Effects of botulinum toxin A on the dystonia by various dosage of injection. *Chin J clin Rehabil*, 2002; 6(18): 2701-2702.

(Originally published in Chinese Journal of Clinical Rehabilitation, 2003; 7(2): 260-261)