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Efficacy of type a botulinum toxin injections and infrared polarized light on treating chronic migraine

J.-H. SONG, G.-B. ZHANG, X.-D. DING, L. HUANG, Y. HONG, H.-X. CHEN

Department of Neurology, Xiangyang Hospital Affiliated to Hubei University of Medicine, Xiangyang, Hubei, China

Jinhui Song and *Guibin Zhang* contributed equally to this work

Abstract. – OBJECTIVE: To investigate the clinical value of the combination of ultrasound-and-hyponome-guided type A botulinum toxin injection and infrared polarized light on treating chronic migraine.

PATIENTS AND METHODS: Ninety-one patients with chronic migraine were randomly divided into four groups: in the control group (group A, 22 cases in total), nimodipine was used in the treatment of chronic migraine for two months; in the infrared polarized light therapy group (group B, 22 cases in total), infrared polarized light was adopted in the treatment of chronic migraine for 50-60d; in the botulinum toxin treatment group (group C, 24 cases in total), ultrasound-and-hyponome-guided type A botulinum toxin was injected into frontal, temporal, and occipital muscles in treating chronic migraine; in the joint treatment group (group D, 23 cases in total), ultrasound-and-hyponome-guided type A botulinum toxin injection in group C and infrared polarized light in group B were both used here in the treatment of chronic migraine. Infrared polarized light therapy lasted 50-60d and the time of study lasted six months. The survey would include the conditions of patients with chronic migraine three months before treatment and at one, three and six months after treatment. Patients were asked to fill the MIDAS (migraine disability assessment questionnaire) and were graded on the evaluation scale of life quality, so that the researchers would be able to compare attack frequency, duration of attack, attack severity, the use of painkillers and their recovery from chronic migraine, and then observe their adverse reactions.

RESULTS: Eleven cases dropped out during the treatment, three cases in A group, two cases in group B, four cases in group C and two cases in group D. One, three and six months after treatment, the MIDAS scores in group A, B, C and D were significantly lower than before the treatment. Hence, the differences were statistically significant ($p < 0.01$). The scores in quality of life rating scale were significantly higher than pre-treatment scores, so the difference was statistically significant ($p < 0.01$). The MIDAS scores and quality of life rating scale scores in group D were compared with those in group A, B, and C respectively, and the differences were statistically significant ($p < 0.05$). Two patients were recorded with dizziness, and the dizziness disappeared after two weeks with no treatments at all. Forehead lines and crow's feet of 21 patients shallowed or disappeared in varying degrees after the injection.

CONCLUSIONS: The combination of ultrasound-and-hyponome-guided type A botulinum toxin injection and infrared polarized light on treating chronic migraine demonstrated a significant clinical effect.

Key Words:

Echo-Doppler, Color-Doppler, Ultrasound, Intervention, Migraine, Botulinum A-type toxin, Infrared polarized light.

Introduction

Migraine is a common neurovascular disease. The clinical manifestations included paroxysm, lateralization, moderate severity, pulsating headaches, nausea, and vomiting. Sound or light stimulation or daily life can aggravate migraines[1-4]. The clinical manifestations of chronic migraine (CM) are that headache attacks appear more than 15d per month for three consecutive months or more. But the headaches caused by drug overdose are excluded. Currently, ordinary drugs against CM have poor efficacy. Foreign studies[5-6] on type A botulinum toxin (BTX-A)

Corresponding Author: Xudong Ding, MD; e-mail: dingxd1018@163.com

ended in different conclusions. Studies on infrared polarized light on treating CM were also rarely reported. In this study, the combination of ultrasound-and-hyponome-guided type A botulinum toxin injection and infrared polarized light on treating CM of 91 cases has achieved a positive outcome.

Patients and Methods

General Information

Inclusion criteria: (1) Patients must meet the diagnostic criteria of the International Headache Society in 1988[7]; (2) The history of migraine attacks was more than six months; (3) The headaches attacked over twice in a month; (4) The headache symptoms (seizure frequency and severity) were relatively stable; (5) The medication of patients was relatively fixed within six months; (6) The abnormities were not found in the CT and MRI examination; (7) The procedure was approved by the hospital Ethics Committees, and all patients signed the informed consent.

Exclusion criteria: (1) other kinds of diseases caused the headaches; (2) Patients with myasthenia gravis, Eaton-Lambert myasthenic syndrome, motor neuron disease, allergies, pregnancy and severe heart, liver, kidney dysfunctions; (3) Patients with serious cognitive function disorders, psychotic disorders or a history of asthma; (4) Patients with fever or infectious diseases; (5) Patients who had used certain drugs that aggregated the neuromuscular transmission disorder.

Ninety-one patients with CM, who came to the department of neurology for treatment from January 2009 to December 2010 and met the above standards, were selected to participate in the study. Patients included 26 males and 65 females, aged from 19 to 45 years old and their mean age was 36.9 years old. The disease duration was from 1 to 9 years, and the average was 6.5 years; 15 patients suffered nausea, vomiting, photophobia or sound sensitivity during migraine attacks. Twenty cases needed painkillers when headaches occurred. All patients underwent pre-treated blood routine, urine routine, liver and kidney function, ECG, and EEG tests. They were randomly divided into four groups. For the control group (group A, 22 cases in total), nimodipine was used in the treatment of CM; for the infrared polarized light therapy group (group B, 22 cases in total), infrared polarized light was adopted in the treatment of CM; For the botulinum toxin treatment group (group C, 24 cases in total), BTX-A was adopted in the treatment; For the joint treatment group (group D, 23 cases in total), BTX-A in group C and infrared polarized light in group B were both used here in the treatment of CM. Differences of gender, age and pain intensity in these groups showed no statistical significance ($p > 0.05$) and these groups were at comparable scales. See details in Table I.

Treatment Methods and Follow-up

Control group: Nimodipine tablets 30 mg, three times a day for a course of two months. Phototherapy group: BPM-III-1 infrared polarized light therapy instrument, with irradiation of the migraine part. The power controlled in 70%-80%; time ratio of intermittence and irradiation was 2: 3, time of irradiation on each point was 5-6 min, one time a day, 5-6 points in one time and 30 min in total, 10 times as a course of treatment and 5-6 courses in total. Botulinum toxin group: BTX-A used in injection was lyophilized crystalline product (Lanzhou Institute of Biological Products), each containing 100 U and placed in 2-8°C refrigerator. Before the injection, it was diluted with saline to 25 U/ml and injected with 1ml syringe in the frontal, temporal, and occipital muscles, with the injection point spacing 1-2 cm. The injected dose of each point was 5U and the total dose was usually (7520) U. Mixed group: BTX-A pain point intramuscular injection and infrared polarization were both adopted. The method was the same for the phototherapy group and botulinum toxin group, with 5-6 courses in total.

Ultrasound-guided procedure[8]: (1) Proper posture, the patient should lie supine; (2) Use iodophor to disinfect the injection site of the skin and apply a proper amount of coupling agent to the skin when it becomes dry; (3) Fill the syringe with about 50ml saline and inject into the water sac. Place it between the probe and the skin so as to improve the clarity of the ultrasound image; (4) Under the guidance of ultrasound location map, find the muscle for injection and cross-sectional area and confirm the injection point and dose; (5) Insert the needle next to the probe and inject BTX-A accurately into the selected muscle. Under the direct vision of ultrasound, inject in a stratified way in accordance with the thickness of the muscle (2 or 3 layers) and pay attention to avoid blood vessels and nerves.

Before the injection, patients would be asked to fill the Migraine Disability Assessment Questionnaire (MIDAS)[9] and health survey (SF-36)[10],

Table I. General conditions of patients with chronic migraine in the four groups.

Group	Case No	Gender (case)		Age	Disease duration (year)	Attack part (case)			Pre-symptom (case)		Part (case)		Seizure frequency (d)	Time of duration (h)	Pain simulation (score)
		male	female			Temporal	Orbital part	Occiput	Yes	No	One side	Two sides			
Group A	22	6	16	37.7 ± 8.2 36.9 ± 7.9	6.4 ± 0.9	12	8	2	4	18	7	15	17.2 ± 3.6 18.5 ± 4.1	7.2 ± 2.6	4.3 ± 1.6
Group B				38.2 ± 8.1	6.3 ± 0.7								19.2 ± 3.9	6.9 ± 2.4	4.0 ± 1.5
Group C	22	7	15		5.9 ± 0.6	13	6	3	3	19	8	14	18.7 ± 3.8	7.0 ± 2.5	4.1 ± 1.3
Group D	24	6	18	36.5 ± 8.0	6.1 ± 0.8									7.1 ± 2.2	4.2 ± 1.5
	23	7	16			11	9	3	4	19	8	15			

so as to score and record the conditions for CM, such as severity, duration of attack, seizure frequency, associated symptoms and the use of painkillers. One month after injection, patients were followed up to get further information about the index above and then, the clinical follow-up or telephone follow-up would be conducted monthly.

Standard Evaluation

Take the onset three months before treatment at the basic level and then compare it to the condition after treatment. According to the severity of CM, seizure duration, seizure frequency, the improvement of associated symptoms and the use of painkillers, use MIDAS and SF-36 score to measure the pain and life quality of patients before and one, three and six months after treatment. Observe the efficacy of CM and evaluate the safety of the treatment by detecting the indicators such as EKG, liver and kidney functions. The MIDAS questionnaire includes five questions, enquiring patients about days when patients are disturbed by headaches in the daily life or work in the past three months. It would be scored in the number of days; SF-36 assesses the quality of life in eight areas, including physical functioning, role physical, bodily pain, general health, vitality, social function, emotional role and mental health.

Statistical Analysis

The data in this study would be in the form of s and analyzed by SPSS (13.0 version, SPSS Inc., Chicago, IL, USA) statistical software package. Two test compared count data, and t test compared measurement data. If $p < 0.05$, then the differences would be statistically significant.

Results

Eleven cases dropped out due to relocation and job transfers during the six-month period. These included three cases in the control group, two cases in the phototherapy group, four cases in the botulinum toxin group and two cases in the mixed group. Eighty patients in total finished the follow-up study (Table II).

Compare MIDAS and SE-36 Scores Before and After Treatment

The MIDAS scores of the patients in the four groups after one, three and six months treatment

were significantly lower than before treatment. Hence, the differences were statistically significant ($p < 0.01$). The SF-36 scores were significantly higher than before treatment, and the differences were also statistically significant ($p < 0.01$). The MIDAS and SE-36 scores in the mixed group after treatment were compared with the remaining three groups at the same time respectively. The differences were statistically significant ($p < 0.05$) (see Table II).

Clinical Efficacy Analysis Before and After Treatment

As for the 80 cases of CM patients after treatment, the seizure frequency was much lower than the basic level before treatment. This difference was statistically significant ($p < 0.01$). The duration of each episode was significantly shorter than the basic level before treatment. The difference was also statistically significant ($p < 0.01$). Painkillers used after treatment was significantly reduced compared with that before treatment, and the difference was statistically significant ($p < 0.01$).

Treatment of Adverse Reactions

Patients in group B showed no significant adverse reactions. Two cases reported dizziness in group C and recovered after one week without any treatment. Forehead lines and crow's feet of 10 patients in this group shallowed or disappeared in varying degrees after the injection; the same situation appeared in group D, forehead lines and crow's feet of 11 patients shallowed or disappeared in varying degrees after the injection.

Discussion

Chronic migraine[11-12] is a common chronic neurological, vascular disease, and the incidence rate is 5%-10%. It is characterized by paroxysmal and moderately severe throbbing headaches, which lasts 4-72h and accompanied by nausea and vomiting. Sound or light stimulation can aggravate the pain, but the quiet rest can ease the pain.

Clostridium botulinum secrets BTX-A during reproduction[13-14]. It can disturb the excitatory neurotransmitter and is used to treat muscle spasms, opisthotonus, cerebral palsy and strabismus clinically. Up to now, there are many clinical studies[15-16] abroad on the efficacy of BTX-A

Table II. Scores of MIDAS and SF-36 in the four groups before and after the treatment (score, $\bar{x} \pm s$).

	Case	Before treatment		One month after treatment		Three months after treatment		Six months after treatment	
Group	No.	MIDAS	SF-36	MIDAS	SF-36	MIDAS	SF-36	MIDAS	SF-36
Group A	19	68.4 ± 12.5	33.6 ± 13.1	53.2 ± 9.3[ab]	80.6 ± 10.6[ab]	37.9 ± 7.1[ab]	78.3 ± 9.1[ab]	41.6 ± 9.0[a]	74.5 ± 8.4[a]
Group B		67.5 ± 11.3	32.8 ± 11.1	51.7 ± 8.1[ab]	82.6 ± 9.4[ab]	35.9 ± 6.4[ab]	79.5 ± 8.3[ab]		
Group C	20	68.1 ± 12.7	32.6 ± 12.4	47.2 ± 7.9[ab]	83.1 ± 10.1[ab]	33.9 ± 5.0[ab]	82.1 ± 8.6[ab]	39.5 ± 8.0[a]	75.5 ± 8.2[a]
Group D	20	67.6 ± 13.1	31.3 ± 12.7	40.5 ± 7.4[a]	89.6 ± 9.4[a]	27.2 ± 3.4[a]	87.3 ± 7.2[a]	37.6 ± 6.3[a]	77.5 ± 7.4[a]
	21							30.3 ± 4.5[a]	82.5 ± 5.6[a]

Note: compare before treatment, [a]$p<0.01$; simultaneous compare with the mixed group (Group D) [b]$p<0.05$.

treatment for CM, but the conclusions are inconsistent. And few studies are reported on the combination of BTX-A and infrared polarized light on treating CM.

In this study, the MIDAS scores in group B and group C after treatment were greatly lower than before the treatment. The difference was statistically significant ($p < 0.01$). The SF-36 scores were significantly higher than before treatment, and the differences were also statistically significant ($p < 0.01$). These indicated that infrared polarized light therapy and BTX-A treatment can both relieve pain in patients with CM, and the quality of life improved. Twenty-one cases received BTX-A injections combined with infrared polarized light therapy. After six months follow-up, we found that, when compared with the other three groups at the same time, the MIDAS scores in the mixed therapy after one, three and six months treatment were significantly lower than that in the other three groups. The difference was statistically significant ($p < 0.05$). The SF-36 scores were in the opposite trend, and the difference was also statistically significant ($p < 0.05$). This indicated that the mixed therapy was better than the infrared polarized light therapy, BTX-A treatment and the control group alone. It could obviously relieve CM pain, significantly reduce seizure frequency, alleviate the severity of headache attacks, shorten the duration of the episodes and improve the physical and mental state and life quality of patients, which indicates that the mixed treatment was better. What is more, the mixed therapy, which was combined with the advantages of multi-modal therapy, resulted in superimposed therapeutic effect. Infrared polarized light therapy or BTX-A treatment alone worked slowly, the former usually took 5-7 times and the latter usually took 7-10d. The peak of efficacy would appear at one month later. But the mixed therapy worked in about 5-7d and the analgesic effect was better than infrared polarized light therapy alone.

The mechanism of BTX-A treatment of CM was not yet identified[17-19]. It might work possibly in the following ways: (1) BTX-A blocked SNARE protein to reduce the effect of muscles on muscle spindles and then produced analgesic effect[20]; (2) BTX-A inhibited the release of neuropeptides (CGRP, P substance), suppressed neurogenic inflammation and reduced the inputting of impulses[21-22]; (3) BTX-A was inputted into the central nervous system, regulated P substance directly, inhibit the vitality of nerve-vascular system and influence the central pain modulating system so that it could relieve headaches[23]; BTX-A may alleviate CM through a variety of mechanisms, which needed further study. Infrared polarized light therapy acted on stellate ganglion, which could dilate blood vessels, improve blood circulation, inhibit the excitability of the sympathetic nervous and block the vicious cycle of the pain; when the pain point was exposed to the polarized infrared light, it can change the vascular permeability, decrease the exudation rate and level of the inflammatory substances and ease congestion and edema; at the same time, it could also diastole local blood vessels, accelerate blood flow and promote absorption of inflammatory substances and the dissipation of inflammatory cells. Thereby, the pain was eased[24].

As a new technology for positioning the injection site, ultrasound was non-invasive and painless with high resolution[25-27]. Nerves and blood vessels in and around the target muscle could be clearly imaged. Muscles in the ultrasound were hypoechoic, tendon was as tubular hyperechoic lines (threadiness) and fascia were hyperechoic. The ultrasonic wave with high frequency was at high resolution and the nerves and blood vessels in and around the target muscle were clearly visible. The water sac could reduce the impact of the probe on the tip, fix the position of the needle and the skin and improve the clarity of ultrasound image. It was very easy to make a water sac. Hence, the water sac could be widely used in clinical practice. In this study, color Doppler ultrasound could fully meet the positioning requirements. And using this device, the operator could locate the needle in an accurate way, not only reaching the target muscles, but also avoid the surrounding blood vessels and nerves.

At present, a large number of clinical studies have not found that BTX-A treatment combined with infrared polarization could cause systemic or serious adverse reactions. In this study, two cases reported dizziness. But it disappeared after two weeks without any treatment. Forehead lines and crow's feet of 21 patients shallowed or disappeared in varying degrees after the injection.

Most chronic headaches are transformed from migraine[28-29]. But no drug can control all kinds of migraines. Due to the high cost of BTX-A injections, botulinum toxin is not recommended for the treatment of acute migraine. But when the conventional drugs are in poor control effect on CM, or accompanied by contraindications, or there are many complications

such as migraine intramuscular dystonia, facial muscle spasms and muscle tension headaches, botulinum toxin, and its mixed therapy can be taken into consideration.

Conclusions

BTX-A combined infrared polarized light therapy can significantly and quickly relieve the pain and improve the quality of life of patients. It has less adverse reactions, and the method is safe, effective and simple, which can be used as a new way in the treatment of CM when part of drugs are in poor effects. Further studies in large samples and multi-centers are needed in the clinical application.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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