

Ultrasound guided injections of botulinum toxin type A into stellate ganglion to treat insomnia

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Abstract. The aim of the study was to investigate the curative effect of botulinum toxin type A (BTX-A) injection into stellate ganglion under ultrasound guidance in patients suffering from insomnia. From October 2015 to April 2016, 48 patients suffering from insomnia were enrolled in this study. Patients were divided into 2 groups using a random digital grouping method: i) Control group (24 cases), and ii) treatment group (24 cases). Patients in the control group received 1 mg oral estazolam 30 min before sleep every night, while patients in the treatment group received BTX-A injection in bilateral stellate ganglions under ultrasound guidance. Curative effect evaluation was carried out after treatment. The international Pittsburgh Sleep Quality Index (PSQI) and polysomnogram (PSG) were evaluated in the two groups before and after treatment. The total effective rate was obviously higher in the treatment group. The PSQI score and the results of the PSG indicated that the insomnia situation improved in both groups. However, compared with the control group, the treatment group had a more significant improvement. In conclusion, BTX-A injection in stellate ganglion was a relatively easy and effective way to treat insomnia without any notable adverse reactions.

Introduction

Insomnia is a common form of sleep disorder characterized by difficulty in falling and staying asleep. In individuals suffering from this condition, sleep quality or quantity cannot reach normal requirement (1). Insomnia can be caused by psychiatric and medical conditions, and unhealthy sleep habits. Chronic insomnia may seriously affect patients' physical

as well as psychological health and can lead to decrease of attention, judgment impairment, loss of memory, anxiety and depression (1). Unhealthy lifestyles and sleep habits can create insomnia or exacerbate the insomnia problem worse.

In the treatment of insomnia, non-benzodiazepine hypnotic drugs are the first line of management followed by benzodiazepines, amitryptiline and antihistaminics. However, these medications can create short- and long-term adverse effects, including drug dependence, addiction and withdrawal reaction (2). In the present study, we investigated the curative effect of botulinum toxin type A (BTX-A) on patients suffering from insomnia, by injecting BTX-A into stellate ganglion under ultrasound guidance, and obtained promising results.

Materials and methods

General data. From October 2015 to April 2016, 48 cases of insomnia were enrolled in the present study. There were 20 males and 28 females (Table I). All the patients suffered from different levels of insomnia symptoms, including difficulty to fall asleep, drowsiness, early awakening, anxiety and physical problems. Inclusion criteria for the study were: i) Patients who complied with the insomnia diagnostic criteria provided by the sleep disorder group of Neurology Branch of Chinese Medical Association, and were given confirmed diagnosis by more than two specialists; ii) patients with Pittsburgh Sleep Quality Index (PSQI) score ≥ 14 ; iii) patients not taking hypnotic drugs within 4 weeks prior to their enrolment; and iv) patients with a maximum of 9 years of education.

Exclusion criteria for the study were: i) Patients with transitory insomnia or insomnia caused by environmental changes; ii) known alcoholics and drug addicts; iii) pregnant and lactating women, and those suffering from serious physical illnesses and neuropsychic diseases; and iv) patients who did not complete the follow-ups.

All the patients signed informed consent forms. The study was approved by the Ethics Committee of Xiangyang No. 1 People's Hospital, Hubei University of Medicine (Hubei, China).

Treatment methods. Patients were divided into 2 groups using a random digital grouping method: i) Control group (24 cases) and ii) treatment group (24 cases). Patients in the control group received 1 mg oral estazolam 30 min before sleep every night, while patients in the treatment group received BTX-A injection

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Table I. Comparison of general data in patients.

Items	Control group	Treatment group	Test value	P-value
Case	22	23	(t/ χ^2)	
Age (years)	55.62±8.35	56.54±9.23	-0.350	0.728
Sex (male)	9 (67.3%)	10 (67.5%)	0.030	0.862
Course of disease (years)	4.24±1.37	4.10±1.18	-1.000	0.715
Diabetes	5 (30.8%)	4 (27.5%)	0.200	0.655
Hypertension	8 (23.1%)	9 (20.0%)	0.037	0.848
Heart disease	3 (48.1%)	2 (50.0%)	0.278	0.598
Education level (years)	12.62±2.38	12.21±2.87	-1.000	0.606
PSQI total points	17.43±2.42	16.38±2.32	-1.000	0.145

PSQI, Pittsburgh Sleep Quality Index.

in bilateral stellate ganglions under ultrasound guidance. For the injection, patients were required to be in a supine position with contralateral head turning. After routine disinfection of skin, puncture needle no. 7 was inserted perpendicularly through the sixth vertebral transverse. The needle was then withdrawn a little, needle tail inclined to the head end at 45°, and the needle head was passed through the front of the sixth vertebral transverse and advanced ~1 cm towards the direction of the seventh vertebral transverse. In case of resorption without blood or cerebrospinal fluid, local anesthetics were administered.

Observation methods

PSQI. PSQI scale included 7 indexes: i) Sleep quality; ii) time for falling asleep; iii) sleep time; iv) sleep efficiency; v) sleep disorder; vi) hypnotic drugs; and vii) daytime functions. Each index was scored as 0-3 scores, with 0 for no difficulty, 1 for mild difficulty, 2 for moderate difficulty and 3 for severe difficulty. Total PSQI scores were the sum of all the scores, with the total score ranging from 0 to 21 scores. A total score of ≥ 7 represented the existence of sleep disorder and higher PSQI scores were associated with lower sleep quality (3).

Polysomnogram. The Alice 4 polysomnography system (Respironics Inc., Murrysville, PA, USA) was used to conduct polysomnogram (PSG) detection. EEG lead used C4/A1 and C5/A2, EMG electrodes were placed at chin, and EOG electrodes were placed at 1 cm from the outer canthus of both eyes. Patients were tested separately in a quiet, comfortable and lightproof sleep lab. PSGs were recorded starting from the second night. When the sleep record did not reflect the situations of usual sleep, data were discarded (4). Sleep staging criteria referred to the International Standards for Polysomnographic Recording and Staging formulated by American Rechtschaffen and Kales (5). The observation indexes included: i) Sleep process; sleep latency (SL), arousal time (AT), arousal wake up of time (AWT), rapid eye movement (REM) latency (RL), sleep efficiency (SE) and total sleep time (TST); and ii) sleep structure included no REM (NREM) sleep and REM sleep. NREM included four stages, namely S1, S2, S3 and S4. The percentage of each stage from the total sleep time was calculated. Both S3 and S4 belonged to deep sleep and were combined into one.

Evaluation of therapeutic effects. According to the subjective feelings of patients, the therapeutic effects were judged in accordance with the evaluation standards for therapeutic effects on insomnia specified in the Amended Draft of Standards for Therapeutic Effects of Mental Diseases (6). Healing was achieved when the sleep condition was significantly improved, when the patient slept 6-8 h sleep/night and enjoyed deep sleep and was full of energy during the next day. We considered that the treatment had a significant effect when the patient slept 3-5 h sleep/night and associated symptoms were disappeared or obviously reduced. Treatment was considered effective when sleep condition was improved and the sleep time was prolonged up to 2 h. When sleep condition and associated symptoms were not improved at all or the improvement failed to reach the standards to be considered effective, treatment was considered to be non-effective.

Observation results. Patients in both groups were subjected to PSQI assessment and PSG test before and after treatment. An assessment of curative effect of treatment was carried out after treatment.

Statistical analysis. We used SPSS 17.0 software (Chicago, IL, USA) for our statistical analysis. Measurement data were expressed as mean \pm SD and comparison between groups was completed with the t-test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of general materials. From 48 patients who were enrolled in this study, three cases were excluded after the beginning of the experiments due to various reasons. Consequently, the study 22 cases in the control group and 23 cases in the treatment group were continued. Differences in patients' general characteristics in the two groups had no statistical significance and were comparable (Table II).

Curative effect evaluation. After being treated for 4 weeks, the total effective rate in the treatment group was obviously higher than that of the control group and the difference was statistically significant ($P < 0.05$). The total effective rates

Table II. Comparison of postoperative curative effect in the two groups.

Groups	Cured	Markedly effective	Effective	Ineffective	Effective rate (%)
Control (22 cases)	2	5	8	7	68.18
Treatment (23 cases)	5	9	6	3	86.95

Table III. Comparison of PSQI score in the two groups before and after treatment (mean \pm SD).

Groups	Case	PSQI total points	Sleep quality	Time for falling asleep	Sleep time
Control					
Before treatment	22	17.43 \pm 2.42	2.61 \pm 0.46	2.65 \pm 0.59	2.56 \pm 0.55
After treatment	22	13.06 \pm 1.82 ^a	1.82 \pm 0.38 ^a	1.93 \pm 0.48 ^a	2.18 \pm 0.38 ^a
Treatment					
Before treatment	23	16.38 \pm 2.32	2.58 \pm 0.37	2.59 \pm 0.45	2.62 \pm 0.52
After treatment	23	10.15 \pm 1.90 ^{a,b}	1.33 \pm 0.35 ^{a,b}	1.63 \pm 0.32 ^{a,b}	1.74 \pm 0.48 ^{a,b}
Groups	Case	Sleep efficiency	Sleep disorder	Hypnotic drugs	Daytime function
Control					
Before treatment	22	2.52 \pm 0.48	2.51 \pm 0.66	2.65 \pm 0.37	2.66 \pm 0.35
After treatment	22	2.02 \pm 0.39 ^a	2.02 \pm 0.38 ^a	2.33 \pm 0.28 ^a	1.98 \pm 0.48 ^a
Treatment					
Before treatment	23	2.62 \pm 0.37	2.64 \pm 0.47	2.59 \pm 0.35	2.60 \pm 0.47
After treatment	23	1.60 \pm 0.41 ^{a,b}	1.33 \pm 0.35 ^{a,b}	1.83 \pm 0.42 ^{a,b}	1.59 \pm 0.38 ^{a,b}

Compared within group before and after treatment, ^aP<0.05; comparison of the treatment group with the control group, ^bP<0.05. PSQI, Pittsburgh Sleep Quality Index.

Table IV. Comparison of sleep process indicators in the two groups before and after treatment (mean \pm SD).

Groups	SL (min)	AWT (min)	AT (time)	RL (min)	SE (%)	TST (min)
Control (n=22)						
Before treatment	60.92 \pm 22.18	120.73 \pm 70.50	7.16 \pm 2.41	112.83 \pm 32.39	61.43 \pm 11.43	234.28 \pm 62.24
After treatment	42.39 \pm 21.35 ^a	102.25 \pm 60.48	5.24 \pm 2.18 ^a	81.08 \pm 37.48 ^a	78.45 \pm 7.08 ^a	302.59 \pm 58.93 ^a
Treatment (n=23)						
Before treatment	59.82 \pm 23.16	121.78 \pm 72.57	7.47 \pm 2.26	110.80 \pm 32.43	60.42 \pm 10.12	232.42 \pm 66.73
After treatment	25.78 \pm 10.08 ^{a,b}	48.5 \pm 19.40 ^{a,b}	3.55 \pm 2.42 ^{a,b}	65.62 \pm 23.68 ^{a,b}	89.53 \pm 6.85 ^{a,b}	385.16 \pm 52.27 ^{a,b}

Compared within group before and after treatment, ^aP<0.05; compared with the treatment and control groups, ^bP<0.05. SL, sleep latency; AWT, arousal wake up of time; AT, arousal time; RL, rapid eye movement latency; SE, sleep efficiency; TST, total sleep time.

in the treatment and control groups were 86.95 and 68.18%, respectively (Table II).

Comparison of PSQI score of patients in the two groups before and after treatment. After 4 weeks of treatment, the PSQI score indicated that the insomnia situation was improved in both groups. However, compared with the control group, the treatment group had a more significant improvement. The difference was statistically significant (P<0.05) (Table III).

PSG results. After 4 weeks of treatment, PSG monitoring results showed that the insomnia condition improved in both groups, but the improvement in the treatment group was more obvious. The difference was statistically significant (P<0.05) (Tables IV and V).

Discussion

Sleep disorder refers to a reduction of sleep time or sleep quality caused by difficulties associated with falling asleep,

Table V. Comparison of sleep structure index in the two groups before and after treatment (% , mean \pm SD).

Groups	NREM			REM
	S1	S2	S3+S4	
Control (n=22)				
Before treatment	23.81 \pm 7.18	55.73 \pm 10.50	9.16 \pm 5.01	11.83 \pm 2.39
After treatment	17.39 \pm 6.05 ^a	20.12 \pm 11.48 ^a	13.24 \pm 4.11 ^a	15.08 \pm 3.48 ^a
Treatment (n=23)				
Before treatment	27.82 \pm 7.16	56.48 \pm 11.37	9.17 \pm 4.06	13.80 \pm 7.43
After treatment	8.78 \pm 3.08 ^{a,b}	46.22 \pm 8.42 ^{a,b}	19.35 \pm 6.02 ^{a,b}	21.62 \pm 3.68 ^{a,b}

Compared within group before and after treatment, ^aP<0.05; compared with the treatment and control groups, ^bP<0.05. NREM, no rapid eye movement; REM, rapid eye movement.

easy awakening, early awakening and difficulty of getting back to sleep. Numerous factors may lead to sleep disorder, but the most important factors are somatic factors, drug factors, environmental factors, mental factors and human biological clock factors (7). The direct cause of sleep disorder is the abnormalities of neurotransmitter, endocrine and other systems caused by cerebral cortex and vegetative nerve dysfunctions. Sleep disorder treatment is usually focused on recovering and coordinating the function of cerebral cortex as well as inhibiting the excessive hyperexcitability of vegetative nerves. Currently, sleep disorder treatment involves drug therapy, physical therapy, traditional Chinese medicine acupuncture therapy, stellate ganglion block and psychological therapy. There are several problems associated with long-term administration of sedative-hypnotic drugs, including dizziness, loss of strength, drug dependence, addiction and withdrawal reaction. Although single stellate ganglion block showed to be a good treatment for insomnia, its long course of treatment and the high risk of recurrence have caused some concerns. The therapeutic effects of physical, acupuncture and psychological therapies on improving insomnia are uncertain and the risk of recurrence exists.

Stellate ganglion, also known as cervical and thoracic sympathetic ganglion, is mainly fused by cervical sympathetic ganglion 7 and 8, and thoracic sympathetic ganglion 1. A number of studies proved that stellate ganglion is involved in adjusting vegetative nerves, inhibiting nervous excitation, relax mental stress, adjusting the relaxation balance of automatic nervous system, increasing cerebral blood flow and improving sleep (8,9).

In clinic, BTX-A is used for the treatment of strabismus, eye muscle spasm, facial tics, muscle spasm and has obtained good effects. It has been shown that BTX-A can inhibit calcium-dependent ACh transportation and lower the mobility of lipid membrane. Thus, BTX-A can disturb nerve conduction by inhibiting the translocation of synaptic vesicles, the fusion with presynaptic membrane and the release of ACh (10).

In this study, we observed the effects of BTX-A on insomnia by injecting BTX-A in bilateral stellate ganglions. Both subjective evaluation (PSQI and evaluation of therapeutic effects) and objective detection indexes (PSG) results in our treatment group were significantly superior to those of the control group.

These results suggested that the injection of BTX-A in stellate ganglion improved the sleep situations of patients and had definite curative effect on insomnia. The exact mechanism of this curative effect remains unclear, but some suggestions have been made: i) BTX-A may improve the situation by relieving cerebral angiospasm and adjust the balance of vasomotor function. It increases the energy reserves in cerebral cortex nerve cells by boosting aerobic metabolism of brain (11). ii) BTX-A may adjust vegetative nerve functional disturbance caused by the increase of sympathetic nerve activity, improve sympathetic-vagus unbalance and lower the level of plasma norepinephrine caused by it. Thus BTX-A can improve the function of vegetative nerve (12). iii) It has an active two-way regulation function in hypothalamus and generates significant effects on the secretion of hypophyseal hormones. It can regulate the function of automatic nervous, endocrine and immune systems. By regulating the hypothalamic function, BTX-A can maintain the stability of the internal environment and ameliorate the function of the endocrine, immune and vegetative nerve systems. By maintaining the stability of these systems, BTX-A can help patients with insomnia to return to their normal biological clock set up (13). iv) Pineal gland, under the control of sympathetic nerve, periodically secretes melatonin during day and night, which affects sleep and wakefulness. The increased tonicity of sympathetic nerve causes the dysrhythmia of melatonin secretion. The secretion of melatonin is adjusted to correct the disorders of circadian rhythm. Uchida *et al* reported that an increase in the tonicity of sympathetic nerve caused the dysrhythmia of melatonin secretion and stellate ganglion block (5). This situation led to a reduction in sympathetic nerve tonicity and adjusted sleep condition. v) BTX-A inhibits sympathicoadrenal system and lowers the level of epinephrine, cortisol as well as angiotensin II (14) and also adjusts autonomic nerve function.

The surrounding anatomy of the stellate ganglion is very complex. Several key structures such as apex pulmonis, scalene muscle, arteria subclavia, common carotid artery, vertebral artery, internal thoracic artery, inferior thyroid artery, internal jugular vein, brachiocephalic vein, vagus nerve and phrenic nerve can be found around this ganglion. Utmost care must be taken to prevent damage during the injection. In case of carelessness, complications such as local hematoma, pneumothorax

or hemopneumothorax, recurrent laryngeal nerve block, upper extremity palsy and stellate ganglion injuries may occur (15). In this study, all the injections were completed under ultrasound guidance without any adverse reaction.

In summary, results obtained from our study demonstrated that BTX-A injection in stellate ganglion under ultrasound guidance was a relatively easy and effective way to treat insomnia without any notable adverse reaction.

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