Original Article

Efficacy of Carbamazepine Combined with Botulinum Toxin A in the Treatment of Blepharospasm and Hemifacial Spasm

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Abstract

Purpose: To observe the efficacy of the combined treatment of carbamazepine and botulinum toxin A for blepharospasm and hemifacial spasm.

Methods: Fifty-eight patients with either blepharospasm or hemifacial spasm were randomly divided into treatment and control groups. In the treatment group, 30 patients were administered with local intramuscular injections of botulinum toxin A and oral carbamazepine 100 mg/time, 3 times/day for 60 days. Twenty-eight subjects in the control group underwent local intramuscular injections of botulinum toxin A only.

Results: After combined treatment, the complete remission rate was 90%, which was significantly higher than that of the of the control group (67.9%, $P<0.05$, $\chi^2=4.733$). However, no statistical significance was noted regarding the duration of therapeutic effects between the treatment group (range 14~40 weeks; 19.2 weeks on average) and control group (range 12~36 weeks; 18 weeks on average).

Conclusion: The combined therapy of carbamazepine and topical injections of botulinum toxin A had increased efficacy in the treatment of blepharospasm or hemifacial spasm, but had no significant effect in terms of the duration of the therapeutic effect. (***Eye Science 2012; 27:178-181***)

Keywords: carbamazepine; botulinum toxin A; blepharospasm; hemifacial spasm

Primary blepharospasm and hemifacial spasm are a distinct disorders characterized by clonic or tonic contractions of muscles, which can be treated by medicine, acupuncture, physical therapy, local blocking, intracranial-extracranial operations, etc. However, each method has certain limitations in clinical practice. In this study, the combined therapy of carbamazepine and botulinum toxin A presented with relatively high efficacy in the treatment of both blepharospasm and hemifacial spasm.

Clinical information

Inclusion criteria

Subjects with blepharospasm or hemifacial spasm induced by Meige syndrome, essential tremor or Parkinson's were selected to participate in the study. Those with no history of heart, brain, liver, or kidney and drug allergy and capable of completing the planned treatment and subsequent follow-up were enrolled in the study

General materials

Based upon the inclusion criteria, 58 qualified patients with blepharospasm or hemifacial spasm were divided into the treatment and control groups. In the treatment group, the patients were administered with carbamazepine plus local injections of botulinum toxin A. The participants in the treatment group included 13 males and 17 females, from 21 to 68 years and 49.2 years on average. The duration of the disease was between 1.5 and 21 years. Among the participants in the treatment group, 26 were cases of blepharospasm and 4 were cases of hemifacial spasm. In the control group, 28 patients had local injections of botulinum toxin A. The participants included 14 males and 14 females, from 17 to 70 years and 47.8 years on average. The duration of the

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disease was between 0.67 and 34 years. Participants in the control group included 25 cases of blepharospasm and 3 cases of hemifacial spasm. No significant differences were noted between the two groups regarding mean age, sex, or the percentage of blepharospasm and hemifacial spasm (P>0.05).

Grading of blepharospasm and hemifacial spasm

The severity of blepharospasm and hemifacial spasm was graded according to the standard proposed by Shorr et al[1]. Grade 0: no spasm; grade Ⅰ: increased frequency of blink caused by external stimulus; grade Ⅱ: mild spasm, slight tremor of eyelid and no dysfunction; grade Ⅲ: obvious spasm and mild dysfunction; grade Ⅳ: severe spasm and severe spasm and dysfunction (unable to read and drive, etc.). Prior to treatment, the treatment group included 2 cases of grade Ⅱ, 10 cases of grade Ⅲ, and 18 cases of grade Ⅳ. The control group had 3 cases of grade Ⅱ, 13 cases of grade Ⅲ, and 12 cases of grade Ⅳ. No significant difference was found between the two groups regarding the grading of the disease (P>0.05).

Evaluation on treatment efficacy

According to the evaluation criteria proposed by Zhuang Dai et al.[2], the severity of spasm decreased to grade 0 was defined as complete remission; decreased from grade Ⅱ~Ⅳ to grade Ⅰ~Ⅱ was remarkable remission; decreased from grade Ⅳ to grade Ⅲ was partial remission; no apparent changes in the severity of spasm was null.

Clinical treatment

Topical injections of botulinum toxin A

Botulinum toxin A was purchased from the Lanzhou Institute of Biological Products (S10970037); 100 U per unit was kept at 2~8 ℃, diluted by PBS to a concentration of 2.5 U/ml, and 40 U of insulin syringe was used. Multiple injections were administered on the orbicularis oculi muscle and spasmodic muscle intramuscularly or subcutaneously. The injection site were as follows: the inner and outer 1/3 of the upper eyelid; 5 mm from the temporal side of outer canthus for lower eyelid injection; 4 to 5 injection sites for each eye, 2.5 to 5 U per site. In addition to these injections sites, another three sites, including the middle and lower parts of the face and buccal were injected for the patients with hemifacial spasm, with 2.5 to 10 U per injection site. Other injection sites, such as inner/outer sides of eyebrow, upper lip, and lower mandible were selected with a dose of 55 U or below for blepharospasm subjects and 75 U or below for those with hemifacial spasm[2]. At one week after treatment, the patients with residual or recurrent spasm were given additional injections of 5 U for each site; the overall dose in one month was no more than 200 U[3].

The patients in the treatment group had local injections of botulinum toxin A combined with oral intake of carbamazepine, 100 mg/time, 3 times/day for two consecutive months (60 days).

Follow-up and statistical analysis

The patients were followed up by personal visit or phone call for 0.5 to 1.5 years. Parameters including effect time, duration of efficacy, degree of disease remission, and systemic and topical adverse events were compared between the two groups. The data were statistically analyzed by *t*-test and *chi*-square test. P<0.05 was considered statistically significant.

Results

In the treatment group, 27 of 30 cases had complete remission (90.0%; 23 cases of blepharospasm and 4 hemifacial spasm); 3 patients had apparent remission (10%; 3 blepharospasm). Another two patients showed complete remission after additional injections and one case refused additional injections because of the satisfactory outcome. The treatment efficacy began to take effect at 1 to 3 days post injection and endured for 14 to 40 weeks, 19.2 weeks on average.

In the control group, 19 patients (n=28) had complete remission (67.9%; 16 blepharospasm and 3 hemifacial spasm); 9 patients had apparent remission of spasm (32.1%; 9 blepharospasm); among 9 patients with partial remission, 6 had complete remission after additional injections, and 3 maintained apparent remission. In the control group, the injections started to take effect at 1 to 3 days and maintained for 12 to 36 weeks, 18 weeks on average.

The two groups differed significantly regarding clinical efficacy (P<0.05, χ^2=4.733), while no statistical significance was found regarding the duration of

treatment efficacy (P>0.05).

Adverse events. In the treatment group were 3 cases of ptosis, 3 partial closure of eyelid, and 1 distortion of commissure. All symptoms were allayed at 2 to 4 weeks after the additional injections. No systemic disorders were observed in patients in the treatment group. In the control group, 9 cases had headache, drowsiness, nausea, hypodynamia and other systemic disorders. All symptoms were alleviated or eliminated by the end of the treatment. In addition, 1 ptosis, 1 partial closure of eyelid, and 1 lower facial spasm were noted in the control group. Subsequently, all symptoms disappeared at 2 to 3 weeks.

Discussion

Essential blepharospasm is a chronic disease with unknown causes and usually involves bilateral eyes. It frequently attacks middle-aged and elderly women. Essential hemifacial spasm refers to a neurological movement disorder involving involuntary and sustained contractions of the muscles around the eyes, typically involving the orbicularis oculi muscle and gradually extending to other facial muscles on the same side[4], mostly in middle-aged and elderly women. blepharospasm or hemifacial spasm are commonly treated by carbamazepine, phenytoin sodium, haloperidol, clonazepam, etc. Carbamazepine is an inhibitor of voltage-gated sodium channels, typically used for the treatment of seizure disorders and neuropathic pain. It is relatively efficacious for blepharospasm and hemifacial spasm[5].

Botulinum toxin A is a neurotoxin produced by the bacterium Clostridium botulinum. It functions to suppress the release of acetylcholine from the presynaptic membrane of peripheral motor nerve endings, inducing muscular spasm. In previous studies, low dose injections of botulinum toxin were administered at the ocular muscle and lower facial muscle to eliminate or alleviate blepharospasm and hemifacial spasm. In 1984, Fruch et al[4]. first treated blepharospasm and hemifacial spasm by injections of botulinum toxin and gained relative efficacy, which has been widely accepted by many surgeons. Considering its temporary therapeutic effect, repeated injections of botulinum toxin are required. Furthermore, it is difficult to select proper injection sites and manage the injection dose precisely because of the high degree of toxicity and differences in age, severity, and range of spasm. Excessive dose of botulinum toxin might induce unexpected adverse events. Certain patients require additional injections because of unsatisfactory outcomes.

To enhance the efficacy and prolong the duration of remission in the treatment of blepharospasm and hemifacial spasm, we adopted oral intake of carbamazepine combined with topical injections of botulinum toxin, which yielded relatively good results. The patients in the treatment group had a complete remission rate of 90%, which was significantly higher than the 67.9% of the control group. Carbamazepine inhibits sodium and calcium channels in neurons, stabilizes nerve cell membranes, suppresses high-frequency discharge, blocks synaptic transmission, limits the transmission from thalamic ventral anterior nucleus to the frontal lobe[5] and exerts en effective inhibitory effect on exciting blepharospasm and hemifacial spasm. The combined effects of carbamazepine and the lax effects of botulinum toxin yield a high efficacy. No statistical significance was noted between the two groups regarding the duration of effect, indicating that the two-month combined therapy of botulinum toxin and carbamazepine did not differ significantly from botulinum toxin alone regarding the duration of effect. In this study, both the combined therapy and the use of botulinum toxin alone were more efficacious in the treatment of hemifacial spasm than in blepharospasm. Four patients with hemifacial spasm in the treatment group and three with hemifacial spasm received injections of botulinum toxin for the first time and obtained complete remission, which is consistent with the findings of previous studies[4].

Local injection of botulinum toxin might induce certain adverse events by inappropriate injection dose and site during the treatment of blepharospasm and hemifacial spasm, such as blepharoptosis with an incidence of 12%[6], diplopia, exposure keratitis, topical ecchymosis, etc. The occurrence of ptosis is caused by the dissemination of botulinum toxin to the levator muscle. In this study, four patients presenting with ptosis (3 in the treatment group; 1 in the control group) gradually recovered at 2 to 3 days

post injection. It should be noted that the central part of the upper eyelid should be avoided during injection, and the injection dose should be controlled to no more than 25 U. The major action site of botulinum toxin is the nerve ending at the neuromuscular junction. The absorption of botulinum toxin into the blood cycle may induce asthenia, drowsiness, etc. A lethal dose of botulinum toxin for humans is estimated between 2800 and 3500 U[7], whereas the topical injection dose for eyelid and face is less than 100 U, which seldom causes any systemic responses. In this study, no apparent systemic reactions were noted in the patients that received the injections of botulinum toxin. Previous research indicated that long-term or repeated injections of botulinum toxin does not affect its efficacy but significantly decreases the incidence of adverse events[8].

Common adverse events include dizziness, fatigue, drowsiness, ataxia, nausea, vomiting, rash, etc. To prevent the incidence of adverse events, the administration of carbamazepine should be at a lower dose, which should be gradually increased to a maximum dose of 1200 mg/d. In addition, a relatively high dose can increase the treatment efficacy of carbamazepine[5]. The treatment of spasm with medicine has certain limitations, such as poor long-term efficacy and multiple adverse events after long periods of administration. In clinical practice, a simple treatment with long-term efficacy but no severe adverse events is urgently required.

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