

Minimally invasive botulinum toxin type A injection from the ocular surface to extraocular muscles

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Abstract

• **AIM:** To investigate a new, safe and effective injection method for strabismus patients. Botulinum toxin type A (BTXA) was injected by pulling the extraocular muscles with a minimally-invasive technique into the ocular surface, and it was ensured that the extraocular muscles was maintained in the suspended state.

• **METHODS:** A total of 32 patients with different types of strabismus were treated at our institution from February to October 2010. A small conjunctival incision (≤ 2 mm) was made under a microscope. The extraocular muscles were pulled out with a hook to ensure an elevated position compared with the wall of eyeball. The muscle fiber was clearly seen through the conjunctiva and BTXA was injected at a small angle under the microscope. The deviation angles before and after the injection were recorded. All patients were followed up at 5 and 30 days after the operation. Recovery was defined as abolition of diplopia in straight-ahead gaze and anteroinferior gaze and the symptoms of giddiness disappeared thoroughly. Eyeball position was essentially normal. Improvement was defined as basic disappearance of diplopia in straight-ahead gaze and anteroinferior gaze; restriction of action of paralytic muscle improved. If most of the symptoms and signs still existed and disturbed normal work and life, the treatment was determined to be invalid. The injection dose for patients of 5 to 10 prism diopter (PD), 11 to 20PD, and ≥ 21 PD was 1u, 3u and 4u to 5u, respectively.

• **RESULTS:** Of the 32 treated patients, 11 (34.4%) were cured, and 18 (56.3%) were improved at 5 days after the operation; 12 (40%) were cured, and 15 (46.9%) were improved at 30 days. Five patients (15.6%) who had unsatisfactory response after BTXA injection at 30 days received repeated injections or underwent strabismus

surgery. Ptosis was present in 2.5% of the injected eyes. No retrobulbar hemorrhage or ocular perforation was found in any eye.

• **CONCLUSION:** It is safe and efficient to inject BTXA by pulling extraocular muscles with a minimally-invasive technique under the microscope to make the muscles separated from the wall of eyeball.

• **KEYWORDS:** botulinum toxin; paralytic strabismus; microscope

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INTRODUCTION

Botulinum toxin type A (BTXA) injection into the extraocular muscles (EOMs) is an effective alternative to treatment of strabismus besides the use of optical devices (prisms and glasses) and operation^[1]. It can produce a dose-dependent duration of muscle paralysis, which shifts the eye into the field of action of the antagonist muscle. When the medicine worked, it changed the original condition that the paralyzed muscle stretched whereas the antagonist muscle contracted. As the paralysis weakens, the eye will gradually return toward its original position but with a new balance of forces that permanently reduces or eliminates the deviation^[2]. Injections with botulinum toxin are generally well tolerated and there are few side effects. So the therapeutic effect of BTXA on the strabismus is well accepted, but there has not been very maturely commercial electromyograph (EMG) yet. Most surgeons inject BTXA at the point of attachment of a muscle blindly. There is no guarantee that there is sufficient drug reaching the muscle. What is more, it probably increases the risk of scleral perforation because the wall of eyeball is in close contact with EOMs, which affects its application in the treatment of strabismus. The purpose of this study was to investigate a new, safe and effective injection method by pulling EOMs with a minimally-invasive technique into the ocular surface, ensuring that the EOMs were maintained in a suspended state.

MATERIALS AND METHODS

Patients From February to October 2010, 32 patients with different kinds of paralytic strabismus, acute esotropia and Graves ophthalmopathy on account of head trauma, hypertension, diabetes, cerebral infarction, hyperthyroidism and other reasons were treated at our institution. Their average age was 42.5 years (range: 10 to 68 years). There were 15 women and 17 men. All patients were examined in the neurology before injection of BTXA to exclude any intracranial space occupying lesion. No patients had previous eye surgery.

Before treatment, detailed ophthalmic examinations such as eyesight, tonometry, slit-lamp examination of the anterior segment and ocular fundus examination were done. Ocular deviations were evaluated with a prism cover test at a distance of 33cm and 6m respectively. Strabismus degree of 9 azimuth was detected with synoptophore before the injection. We did diplopia test with red and green glasses and passive stretch experiments to the eyeball.

Methods The content of BTXA (Lanzhou Institute of Biological Products, Lanzhou, China) used in this study was 50u for one bottle, dilution with botulinum toxin A 50U plus a certain amount of normal saline according to the desired concentration. In order to control the injection quantity, the drug was diluted at different concentrations according to degree of the external ophthalmoplegia and restriction. Generally, the dosage of each intramuscular injection was less than 0.15mL. With regard to the injection dose of drug, the dose was divided into large, medium and small levels according to the strabismus angle. The patients of 5 to 10 PD was injected with 1u of BTXA; those of 11 to 20 PD was injected with 3u of BTXA; those of ≥ 21 PD was injected with 4u to 5u of BTXA.

0.1mL of 2% lidocaine was used for local anesthesia. A incision of 2mm was made at the side of attachment of EOM under microscope. The conjunctiva and capsule of tenon to sclera were separated. The muscle insertion was exposed. The hook was dipped into the point of attachment of a muscle and the EOM was pulled out. Then the muscle was drawn quietly in the opposite direction from the sclera. The muscle must be stretched tight and keep an elevated place compared with the wall of eyeball. The gap was very small (normally 0.5mm-1mm). The muscle fiber can be identified clearly through the conjunctiva. A needle was inserted at an angle of 15 degrees from the muscle insertion. The distance of travel in the muscle was approximately 10mm. A helper pumpbacked along injecting by the syringe under a microscope until BTXA was injected into the muscle or muscle sheath. The drug was remained in the muscle sheath by increasing drug concentration (50u/mL)

and making the needle through the muscle for a longer distance in the patients who need an injection of large units of BTXA. After the injection, the conjunctival wound was closed with a tweezer. Antibiotic eye ointment was given and the eye was bound up. The entire procedure lasted 3-5 minutes.

In respect of the follow-up, degree of strabismus, eye movement, diplopia situation, binocular visual function and adverse effects were assessed at 5 and 30 days after the operation. In terms of evaluation criteria, recovery was defined as elimination of diplopia in straight-ahead gaze and anteroinferior gaze and the symptoms of giddiness disappeared thoroughly. The eyeball position was essentially normal. Improvement was defined as basic disappearance of diplopia in straight-ahead gaze and anteroinferior gaze; restriction of action of paralytic muscle improved, but still can be detected. If most of the symptoms and signs existed or progressed, but still disturbed normal work and life, the treatment was determined to be invalid.

RESULTS

A total of 32 patients (24 unilateral cases and 8 bilateral cases) were treated by BTXA injection. The types of strabismus included paralytic esotropia (11 cases), paralytic exotropia (8 cases), rectus palsy (5 cases), inferior rectus palsy (4 cases), acute esotropia (1 case) and thyroid associated ophthalmopathy (3 cases). Injected muscles were medial rectus in 16 eyes, lateral rectus in 10 eyes, superior rectus in 7 eyes, and inferior rectus in 7 eyes. The average dose was 2.5u (range, 1.25u to 5u).

Of the 32 treated patients, 11 cases (34.4%) were cured, and 18 cases (56.3%) were improved at 5 days after the operation. Twelve cases (40%) were cured, and 15 cases (46.9%) were improved at 30 days. Five patients (31.8%) who had unsatisfactory responses after the injection at 30 days received repeated injections or underwent strabismus surgery. Ptosis was present in 2.5% of the injected eyes. It was transient and not present at 3 months. Minimal conjunctival hemorrhage was observed at either incision site or the areas of forceps grasping and it was absorbed 1 week after the operation. No retrobulbar hemorrhage, ocular perforation, blurred vision or pupil dilation was observed in any eye.

DISCUSSION

Botulinum toxin is an exotoxin produced by the bacterium *Clostridium botulinum*. It acts on cholinergic nerve terminals and produces the flaccid paralysis of skeletal muscle by blocking the release of acetylcholine at the neuromuscular junction of cholinergic nerves. *C. botulinum* elaborates eight antigenically distinguishable exotoxins (A, B, C1, C2, D, E, F and G). Type A appears to have great

muscle paralytic effect in humans. BTXA plays a very significant role in the treatment of strabismus. By far, the use of BTXA has been expanded to focal dystonias, hemifacial spasm, and various spastic movement disorders, headaches, hypersalivation, hyperhidrosis and facial aesthetics^[1,3].

Scott^[1] first described the characteristics of BTXA and an injection technique with "closed sky" procedures. Injection can ensure the toxin is accurately delivered to the target muscle with the help of EMG-guided placement of the needle. Kao and Chao^[4] thought EMG guidance, although useful for positioning the needle tip precisely, diminished the sensation of the needle tip, inasmuch as the needle used had a long shaft (1.5 inch), which in turn probably increased the risk of scleral perforation. Because EMG guidance was a prolonged procedure, was "noisy", and involved the placement of a long needle in front of the patient's face, patients invariably felt anxious. McNeer *et al*^[5] believed that this maneuver markedly increased the risk of leakage to adjacent muscles. Subsequently Campos^[6] introduced an "open sky" procedure. The conjunctiva was opened with a radial cut parallel to the medial rectus insertion. Botulinum toxin was injected under direct visualization by engaging the muscle on a hook, followed by inserting a 30-gauge needle approximately 10mm from the muscle insertion. With this technique, electromyographic control was not needed. After the injection, the conjunctival wound was closed with an 8-0 Vicryl suture. The whole procedure required 8-12 minutes of anesthetic inhalation. This method had accurate positioning, but damage by operation was larger and conjunctival scars left behind would affect the re-injection or the following operation. There were no advantages of minimal wound and duplicate injection.

Monopolar needle electrode and myoelectricity amplifier designed by Scott were adopted in China. BTXA was injected when the needle was detected in the extraocular muscle^[7]. But this instrument has not been commercial in our country. Clinicians inject the BTXA into the muscle directly by syringe in the treatment of strabismus. This kind of method not only causes an inaccurate dose because of overflowing but also impairs the normal structure of surrounding tissue. Moreover, the patient is in danger of endophthalmitis and scleral perforation. The use of BTXA in squint has been increasing each year. However, the regular apparatus and tool is imperfect. It is necessary to

make the analysis and comparison of different injection methods and find a safe and effective way.

In this study, a small conjunctival incision (≤ 2 mm) was made under a microscope. The surgeon pulled out EOMs with a hook and the drug was injected into the muscle under the microscope. This manipulation has the advantages of short operative time and high position accuracy. The reasons for external ophthalmoplegia or restriction are various. Our method was proved effective for different kinds of strabismus with diverse causes, except for contraction of antagonist muscle. It is not easy to injure the wall of eyeball because of light muscle pulling. Most of the drugs were kept in the muscle or tenon with little adverse reaction. Botulinum toxin injection produces only partial, temporary and mild side effects, including lapsus palpebrae superioris, subconjunctival hemorrhage, effect of the drug on adjacent muscles and so on. At present, ptosis most often happens, because apertor oculi is extremely sensitive to the BTXA. The incidence was reported as from only a few percent to as much as 50%, with an average of 13.4%^[8]. Only one ptosis case was observed in our research. The reason for the low incidence is that the method can ensure the drug remaining in the muscle sheath as much as possible and greatly reduce the possibility of drug extravasation. Minimal subconjunctival hemorrhage was the most common symptom and was absorbed 1 week after the operation. Systemic side effects were not caused in all cases. The small incision under the microscope and drug injection after pulling extraocular muscle upward is a simple, safe, cheap and effective method.

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