• Clinical Research •

Clinical efficacy of botulinum toxin type A on acute acquired comitant esotropia

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Abstract

● **AIM:** To investigate the effects of micro-injection of botulinum toxin A (BTXA) on acute acquired comitant esotropia (AACE).

● **METHODS:** A total of 33 AACE patients who underwent BTXA micro-injection at Renmin Hospital of Wuhan University from September 1st, 2019 to July 1st, 2021 were retrospective analyzed. Esotropia, eye alignment, stereopsis, and complications were examined at baseline (except complications), 1wk, 1, 3, and 6mo after injection.

● **RESULTS:** The average angle of deviation before injection was $(+20.24\pm6.80)^{\Delta}$ at near and $(+24.76\pm6.43)^{\Delta}$ at distance, while $(+5.15\pm5.85)^{\Delta}$ at near and $(+7.30\pm6.17)^{\Delta}$ at distance 6mo after treatment (P<0.05). Six months after injection, the stereopsis of patients had improved. The number of patients having no stereopsis (>800 seconds of arc) decreased from 11 to 3. The number of patients having peripheral stereopsis (300-800 seconds of arc), macular stereopsis (70-200 seconds of arc) and central concave stereopsis (≤60 seconds of arc) increased from 10 to 11, 10 to 12, and 2 to 7, respectively. At the follow-ups at 1wk, 1, 3, and 6mo after injection, success rates were 96.97%, 96.97%, 93.94% and 87.88%, respectively. One week after injection, two patients (6.07%) showed subconjunctival hemorrhage; three patients (9.09%) showed limited eye movement and one patient (3.03%) showed mild vertical strabismus. All the symptoms disappeared by the final follow-up.

● **CONCLUSION:** Micro-injection of BTXA can reduce diplopia and improve binocular vision function of AACE patients. Furthermore, the operation is relatively safe with few complications, making it an ideal treatment modality for AACE.

● **KEYWORDS:** acute acquired comitant esotropia; botulinum toxin A; binocular visual function; stereopsis; diplopia

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INTRODUCTION

Acute acquired comitant esotropia (AACE) is the peculiar type of rhinoptia and it always appears on adults and some older children[1-2]. AACE is often manifested as the sudden onset of esotropia and diplopia, which also seriously affects the patients' quality of life[3]. Patients with AACE usually have normal extraocular motility, no ophthalmoplegia, and no neurological abnormalities[4-5]. AACE used to be considered as an unusual type of strabismus, which accounts for only about 0.3% among strabismus[6]. However, with the rising number of electronic devices and heavy academic stress, the incidence of AACE has increased over decades of years[7-9]. Botulinum toxin type A (BTXA) is a kind of neurotoxin that paralyzes muscles[10]. It has been used to treat various types of strabismus for more than 30y[11-13]. Micro-injection of BTXA into the extraocular muscle has emerged as a new therapeutic modality and an alternative to some strabismus surgeries[14-15]. At present, few studies or reports describe the use of BTXA as a treatment for AACE in either domestic or international contexts.

SUBJECTS AND METHODS

Ethical Approval This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Renmin Hospital of Wuhan University, China (WDRY2020-K211). Informed consent was waived due to the retrospective nature of the study.

Subjects Thirty-three AACE patients' medical records who underwent BTXA micro-injection at Renmin Hospital of Wuhan University from September 1st , 2019 to July 1st , 2021 were retrospective analyzed. Patients who met the following criteria were included in the retrospective study: 1) acute episode of esotropia; 2) diplopia; 3) angle of esotropia

deviation >10 prism diopters (Δ); 4) normal extraocular motility; 5) equivalent deviation (deviation difference $<5^{\Delta}$); 6) no neurological abnormalities.

Patients who have the history of ocular diseases such as ophthalmoplegia, ocular surgery, trauma, amblyopia were not included and those with neurological diseases like myasthenia gravis and pituitary tumor, were excluded too.

All patients were followed up at 1wk, 1, 3, and 6mo after treatment to observe and evaluate esotropia deviation angle, eye alignment, diplopia, stereopsis and any presenting complications.

Methods of Examination Obtain the basic information of every patient, including: 1) personal history (age, gender, occupation); 2) eye use history (daily near working hours, onset process and duration of AACE); 3) past history (previous eye diseases, surgical history, trauma history, and systemic diseases including diseases affecting the neurological and endocrine systems).

Ophthalmic examinations were performed before injection, such as best corrected visual acuity (BCVA), intraocular pressure (IOP), deviation angle of exotropia (both at 33 cm and 6 m), stereoacuity, cycloplegic refraction, and slit-lamp assessment. Spherical equivalents (SE) of refractive error were calculated using the algebraic sum of the dioptric powers of the sphere and half of the cylinder. Oculomotor examination was examined by Hess screen test to determine whether eye movement was limited. The deviation angle was measured by alternate tests with a triangular prism at near (33 cm) and at distance (6 m) fixation. Stereoacuity was assessed with the Titmus test card at 40 cm distance, and results were divided into four levels: no stereopsis (>800 seconds of arc), peripheral stereopsis (300-800 seconds of arc), macular stereopsis (70-200 seconds of arc) and central concave stereopsis (≤60 seconds of arc)[5].

All AACE patients underwent the cranial and orbital computed tomography (CT) or magnetic resonance imaging (MRI) and examined thyroid function and endocrinology teats to exclude neurological and endocrine system diseases.

Treatment The treatment was composed of BTXA (BOTOX, Allergan) in the form of white powdered lyophilized crystals, with each injection containing 100 U. Each unit (1 U) corresponds to an LD_{50} of 0.04 ng when injected intraperitoneally in mice under defined conditions. The compound was diluted with saline and injected into the extraocular muscle belly at the appropriate concentration and dose.

The dosage of BTXA was determined as follows[16-17]: 1.0-2.5 U for esotropia deviation $<+20^{\Delta}$, 12 cases; 2.0-4.0 U for esotropia deviation from $+20^{\Delta}$ to $+40^{\Delta}$, 16 cases; 4.0-6.0U for esotropia deviation $>+40^{\Delta}$, 5 cases.

Effect Evaluation All patients were assessed at 1wk, 1, 3, and 6mo after treatment to evaluate esotropia deviation angle, eye alignment, ocular movements, stereopsis and complications. The treatment was considered effected when diplopia resolved, and residual deviation angle was between -10^{Δ} and $+10^{\Delta}$.

Statistical Analysis SPSS version 25.00 was used for statistical analysis. The Friedman test was used to compare the angle of esotropia deviation across different follow-ups. Mann-Whitney *U* test was used to compare the age and duration of onset, SE, the angle of esotropia deviation pre-injection and the injection dose of the success and failure groups. Fisher's precision probability test was used to compare gender, duration of daily near work and the stereoacuity of the success and failure groups. Cochran's *Q* test was used to compare stereoscopic results across different times. *P* values <0.05 were considered statistically significant.

RESULTS

Characteristics of the Patients A total of 33 AACE patients were included in this study, of which 19 were males, and 14 were females. The mean age was 30.09±10.94 years old (16 to 55 years old). The mean duration of onset was 22.24±15.67mo (6 to 84mo). The mean duration of daily near work before onset was 8.71±1.90h (4.5 to 12h). Of included patients, 25 patients (75.8%) spent more than 8h on near work daily. All patients presented with myopic ametropia, the mean SE of the right eye was -4.54±2.47 D (-1.63 to -13.75 D) and -4.71±2.52 D (-1.50 to -14.00 D) of the left eye. Clinical characteristics are shown in Table 1.

Comparison of Esotropia Deviation Angle Before and After Injection The average angle of esotropia deviation before injection was $(+20.24\pm6.80)^{\Delta}$ at near and $(+24.76\pm6.43)^{\Delta}$ at distance. The average angle of esotropia deviation both at near and at distance at different durations before and after injection are shown in Table 2.

Comparison of Clinical Characteristics Between the Success and Failure Groups Among the 33 patients, 29 (87.9%) were treated effectively and categorized as the success group with the mean esotropia deviation angle six months after injection being $(+3.10\pm1.82)^{\Delta}$ at near and $(+5.21\pm2.24)^{\Delta}$ at distance, respectively. Four patients (12.1%) were categorized as the failure group due to recurrence, and the mean esotropia deviation angle was $(+20.00\pm0.00)^{\Delta}$ at near and $(+22.50\pm2.89)^{\Delta}$ at distance, respectively. The was no significant difference in gender, SE, duration of daily near work, esotropia deviation angle, and stereoacuity before injection. And the difference of injected dose between the success and failure groups was no statistical significance, too. However, the differences in age at onset and duration of onset were statistically significant (*P*=0.048 and 0.030, respectively). The age at onset of the success group was much lower than that of the failure group, and the duration of onset in the success group was much

shorter than that of the failure group. Results showed that the younger at onset and the shorter duration of onset, the better the treatment outcome (Table 3).

Recovery of Eye Alignment in Patients with Different Deviation Angles The injected dose of BTXA varied based on deviation angle, and the 33 AACE patients could be divided into three groups according to deviation angles (Table 4). As deviation angle increased, the injected dose of BTXA also increased accordingly, but success rate at follow-up decreased gradually.

Recovery of Eye Alignment at Different Follow-up Periods The orthotropic ratio was 97.0% (32/33) at follow-up assessment 1wk after injection. One patient, who presented with esotropia deviation angles of $+16^{\Delta}$ at near and $+30^{\Delta}$ at distance before injection, showed evidence of overcorrection after 4 U BTXA injection. The symptom of diplopia disappeared, but the injected eye showed obvious limitation of internal rotation, and the residual deviation angles were -12^{Δ} at near and -18^{Δ} at distance. One month after injection, the orthotropic ratio remained at 97.0% (32/33), since the overcorrected patient had not yet recovered. However, the patient's eye movements were significantly improved in comparison to the previous follow-up. Three months after injection, the orthotropic ratio was 93.9% (31/33). The previously overcorrected patient's eye alignment had been restored to orthotropic position, and the residual deviation angles were -2^{Δ} at near and -2^{Δ} at distance. The two non-orthotropic cases showed recurrence of esotropia. Six months after injection, the orthotropia ratio was 87.9% (29/33). All four cases of non-orthotropia presented with recurrence of esotropia accompanied by diplopia. The remaining patients showed orthotropic eye alignment (Figure 1).

Recovery of Stereoacuity Before and After Injection Comparison of pre-injection status and four post-injection follow-up visits revealed that all 33 patients with AACE in this study presented with improved stereopsis after treatment. The number of patients with no stereopsis decreased, while the number of patients with peripheral stereopsis, macular stereopsis, and central concave stereopsis increased to a statistically significant degree (P<0.05). Before injection, 11 cases had no stereopsis (>800 seconds of arc), 10 cases had peripheral stereopsis (300-800 seconds of arc), 10 cases had macular stereopsis (70-200 seconds of arc) and 2 cases had central concave stereopsis (≤60 seconds of arc). At one week after injection, 8 cases had no stereopsis (>800 seconds of arc), 10 cases had peripheral stereopsis (300-800 seconds of arc), 12 cases had macular stereopsis (70-200 seconds of arc) and 3 cases had central concave stereopsis (≤60 seconds of arc). One month after injection, 5 cases had no stereopsis (>800 seconds of arc), 9 cases had peripheral stereopsis (300-800 seconds of arc), 15 cases had macular stereopsis (70-200 seconds of arc) and 4 cases had central concave stereopsis (≤60 seconds of arc). Three months after injection, the number of patients without stereopsis decreased to 3. The numbers of patients with peripheral, macular, and central concave stereopsis increased to 10, 14 and 6, respectively. Six months post-injection, only 3 patients still had no stereopsis. There were 11 patients had peripheral stereopsis, 12 patients had macular stereopsis and 7 patients had central concave stereopsis.

The percentage of patients who received BTXA injections and showed no stereopsis respectively decreased from 33.3% to 24.2%, 15.2%, and 9.1% at pre-injection, 1wk, 1, 3, and 6mo after injection. Stereoacuity was measured and assessed

Table 1 Clinical characteristics of acute acquired comitant esotropia patients

Variables	n=33
Sex (male:female)	19:14
Age at onset (y)	30.09±10.94
Duration of onset (mo)	22.24±15.67
Spherical equivalent (D)	
Right	-4.54±2.47
Left	-4.71±2.52
Occupation, n (%)	
Students	15 (45.5)
IT staff	5 (15.2)
Accountant	4 (12.1)
Farmer	1 (3.0)
Laborer	2 (6.1)
Unemployed	1 (3.0)
Others	5 (15.2)
Duration of daily near work, n (%)	
<8h	8 (24.2)
≥8h	25 (75.8)
The angle of esotropia deviation pre-injection ($^{\Delta}$)	
Near	+20.24±6.80
Distance	+24.76±6.43
Stereoacuity pre-injection, n (%)	
Stereopsis (+)	22 (66.7)
Stereopsis (-)	11 (33.3)

Table 2 Deviation angles of patients at different durations before and after injection mean±SD

Times	Deviation angles ($^{\Delta}$)	
	Near	Distance
Pre-injection	+20.24±6.80	+24.76±6.43
Post-injection		
1wk	+0.15±2.59	+0.52±3.96
1mo	+1.52±4.02	+2.61±4.39
3mo	+3.30±5.23	+5.18±5.51
6mo	+5.15±5.85	+7.30±6.17
χ^2	115.667	124.644
P	<0.05	<0.05

Table 3 Comparison of clinical characteristics between success and failure groups

Variables	Success group (n=29)	Failure group (n=4)	P
Gender (male:female)	17:12	2:2	1.000[b]
Age at onset (y)	28.76±10.48	39.75±10.50	0.048[a]
Duration of onset (mo)	22.24±15.67	36.00±9.80	0.030[a]
Spherical equivalent (D)			
Right	-4.61±2.62	-4.03±1.64	0.936[a]
Left	-4.66±2.54	-5.03±3.03	0.540[a]
Duration of daily near work, n (%)			0.557[b]
<8h	8 (24.2)	0	
≥8h	25 (75.8)	4 (100)	
The angle of esotropia deviation pre-injection ($^{\Delta}$)			
Near	+19.75± 6.96	+23.75±4.79	0.166[a]
Distance	+24.38±6.58	+27.50±5.00	0.270[a]
Stereoacuity pre-injection, n (%)			0.097[b]
Stereopsis (+)	21 (72.4)	1 (25.0)	
Stereopsis (-)	8 (27.6)	3 (75.0)	
Injection dose (U)	2.88±0.70	3.13±0.47	0.505[a]

[a]Data were analyzed by Mann-Whitney U test; [b]Data were analyzed by Fisher's precision probability test.

Table 4 Eye alignment in patients with different deviation angles mean±SD

Groups	n	Deviation angle pre-injection ($^{\Delta}$)		Deviation angle post-injection 6mo ($^{\Delta}$)		Dose (U)	Success, n (%)
		33 cm	6 m	33 cm	6 m		
≤+20$^{\Delta}$	12	+15.25±6.41	+18.50±6.73	+3.08±5.33	+4.83±5.64	2.17±0.65	12 (100)
+20$^{\Delta}$ to +30$^{\Delta}$	16	+21.75±6.80	+25.63±6.43	+6.06±5.85	+7.94±6.17	3.19±0.68	13 (81.3)
+30$^{\Delta}$ to +40$^{\Delta}$	5	+27.40±7.20	+37.00±6.92	+7.20±4.66	+11.20±4.98	3.80±0.69	4 (80.0)
Total	33	+20.24±6.80	+24.76±6.43	+5.15±5.85	+7.30±6.17	2.91±0.67	29 (87.9)

in patients across five time points using Cochran's Q test, and statistically significant differences in binocular stereoacuity were observed for the five time points (Cochran's Q=22.857, P<0.05; Figure 2).

Complications After Injection One week after injection, two patients (6.06%) experienced a small amount of subconjunctival hemorrhage, which was confined to the bulbar conjunctiva at the injection site and gradually resolved over 2wk. Three patients (9.09%) had limited ocular movement of the injected eye in the nasal direction. Two of these cases were mild (the degree of limitation of medial rectus muscle movement toward the nasal side was -2)[18], and eye movements were in place in all directions by assessment at 1mo after injection. In the other case, symptoms of limited eye movement had significantly improved by 1mo after injection and completely disappeared by three months after injection. One patient (3.03%) showed mild vertical strabismus at follow-up 1wk after injection, and these symptoms disappeared after a month. The other AACE patients had with no special symptoms at every follow-up visit (Table 5).

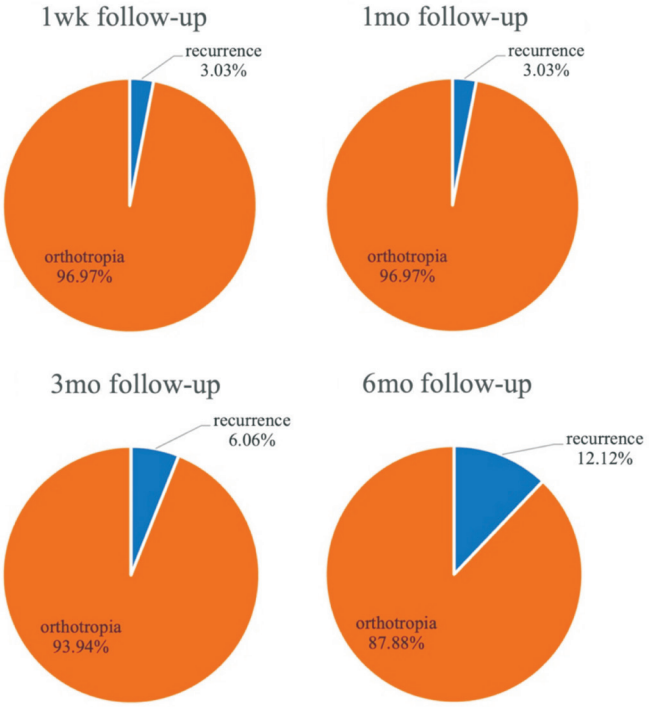

Figure 1 Recovery of eye alignment at different follow-up periods.

DISCUSSION

AACE is a peculiar type of esotropia, primarily occurring in older children and adults[1]. It is manifested as sudden onset of comitant esotropia with approximately the same degree of deviation in all fields of gaze, accompanied by diplopia[19].

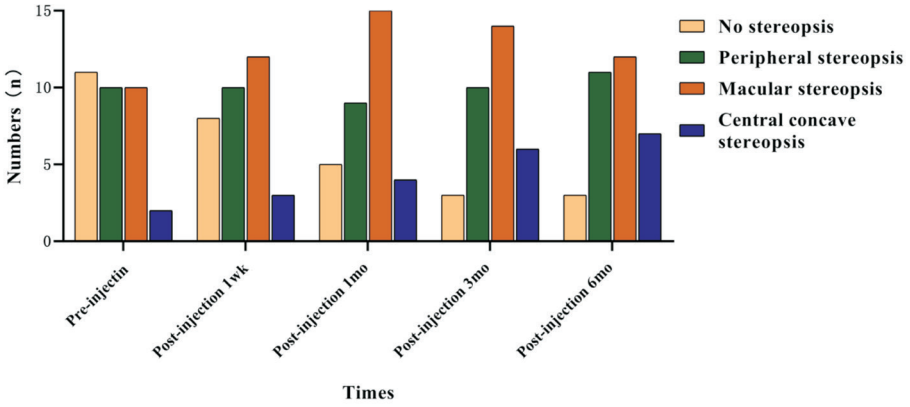

Figure 2 Comparison of stereoacuity in acute acquired comitant esotropia patients before and after botulinum toxin type A injection.

AACE is considered to be an uncommon type of strabismus, accounting for only 0.3% of all the strabismus cases[6,20]. However, with the increasing prevalence of smartphones, Pad, and other electronic devices, as well as the heavier academic pressure on students, the incidence of AACE is gradually rising[21]. Lee *et al*[7] indicated that adolescents with myopia or some susceptible population may induce AACE after excessive use of smart phones at close range. Wu *et al*[22] also confirmed that excessive smartphone use at close range could induce AACE. In our study, we assessed the duration of near work before AACE onset in 33 patients and found that the daily duration of near work before onset ranged from 4.5 to 12h, with a mean duration of 8.71±1.90h. Furthermore, 75.8% (25/33) of patients reported a duration of near work longer than 8h before AACE onset. Prolonged near work leads to excessive convergence, which will increase the tension of the medial rectus. Subsequently, AACE will occur when the separation force is insufficient to overcome the assembly force. According to the clinical characteristics and etiologies described by Burian and Miller[23], AACE can be classified into 3 types: Type I (Swan type) was first proposed by Swan[24] in 1947 and is due to a disruption of fusion resulting from monocular occlusion or visual loss. Type Π (the Burian-Franceschtti type) is characterized by large-angle of deviation and mild hyperopia with no accommodative elements involved and no history of fusion loss. It is usually associated with physical or psychological stress. Type III (the Bielschowsky type) often occurs in patients with myopia ≤-5.00 D or with uncorrected myopia and excessive near work[25].

BTXA is a macromolecular protein that selectively binds to the specific receptor at choline nerve endings[26], which could inhibit the release of the neurotransmitter acetylcholine at the neuromuscular junction, thus resulting in muscle paralysis[27]. In 1973, the American physician Scott[28] first proposed that BTXA had the effect of extraocular muscle paralysis, and it was first used in clinical treatment for strabismus in 1978. When BTXA is injected into the medial rectus of AACE patients, the strength of the injected muscle is weakened for a period of time, rebalancing the muscle strength of the affected eye and, correcting eye alignment and eliminating diplopia[29-30]. In this study, 33 patients opted for BTXA injection as a treatment for AACE. At the final follow-up, 29 patients regained orthotropia, an effective rate of 87.9%, indicating that injection of BTXA can effectively correct patients' eye alignment. The orthostatic rates were 97.0% (32/33), 97.0% (32/33), 93.9% (31/33), and 87.9% (29/33) at follow-up visits 1wk, 1, 3, and 6mo after injection, respectively. The orthostatic rate decreased gradually with prolonged time of follow-up, which may be related to the duration of BTXA effects. The effects of BTXA peaked at 7 to 14d after injection, and most patients showed mild exotropia during this period. As the follow-up period extended, eye alignment gradually returned to a stable baseline. The drug effects remained stable between 1 and 3mo after injection, and eye alignment remained in a relatively stable state. At 3mo post-injection, the effects of the drug began to diminish, and eye alignment gradually began to recede. Six months after injection, the drug effects had essentially subsided. In this study, eye alignment was orthotropic in all patients at the final follow-up, except for four cases of recurrence. Although the direct effects of BTXA at the neuromuscular junction only 4 to 20wk, the maintenance effect of BTXA on eye alignment in clinical practice can extend well beyond 20wk. The mechanisms of this long-term effect are still unclear but may be related to changes in the microscopic anatomy of the neuromuscular junction, recovery and reconstruction of binocular visual function, or remodeling of muscle fibers[31-32]. The specific explanation for this phenomenon requires further investigation.

Table 5 Early complications of botulinum toxin type A injections

Complications	Incidence, *n* (%)
Subconjunctival hemorrhage	2 (6.06)
Vertical strabismus	1 (3.03)
Limitation of eye movement	3 (9.09)
Total	6 (18.18)

Patients with AACE generally present with a short onset time, and the strabismic eye is not yet inhibited. Patients generally have normal retinal correspondence, so the damage to binocular visual function is mild. If treated in a timely fashion, the visual function of both eyes tends to recover well after eye alignment is corrected. In this study, only 11 of 33 AACE patients had no stereoscopic indication before treatment, and only three patients had no stereoscopic indication after treatment. After BTXA injection, stereoacuity was improved compared to pre-injection levels. Patients with AACE who receive timely treatment to eliminate diplopia can avoid reinforcing inhibition of the strabismic eye in the visual cortex of the brain, and timely resolution of factors affecting visual development can allow the restoration of binocular visual function and the restoration or improvement of somatic visual function. Timely removal of factors affecting visual development can restore binocular vision and stereoacuity.

The cost of BTXA injection for AACE is lower than that of operation, and the operation is simple and rapid. The injury of ciliary vessels is less, and fewer complications, such as intraoperative bleeding and postoperative infection, are observed. In addition, when the toxin is injected into the extraocular muscle, there will not be long-term ocular or systemic side effects. Moreover, repeated injections are not recognized by the immune system, so there will not be allergic reaction[32]. However, BTXA injection as a treatment of ACCE still has some finiteness, including the adverse reactions and the limited duration of BTXA action. The most frequent side effect for BTXA injection into extraocular muscles is ptosis[33], which is caused by the spread of BTXA to the adjacent muscles, especially the elevator palpebrae superioris, which is comparatively sensitive to BTXA. No cases of ptosis occurred in the 33 AACE patients probably because the injection procedure was performed under a microscope, and the medial rectus was fully exposed for injection, ensuring that the vast majority of the drug was accurately injected into the muscle belly or myo-synovial sheath. In this study, of the 33 patients injected with BTXA, one case presented with mild vertical strabismus within 1wk after injection but had disappeared by 1mo after the injection. Vertical strabismus may be caused by the leakage of a small amount of drug from the medial rectus belly during injection, diffusion of which to the vertical muscle adjacent to the medial rectus caused denervation of the vertical muscle and paralysis. Since the amount of diffused drug was very small, it manifested as transient vertical strabismus, which disappeared after short time. Among the 33 patients injected with BTXA in this study, three patients developed ocular motility restriction between two days and one-week post-operation, which manifested as limited inward rotation to the nasal direction of the affected eye. In two cases, the restriction was mild and disappeared by 1mo after the injection, and the eye movement was in place in all directions. In the other case, the symptoms of limited eye movement were significantly better one month after the injection, and the symptoms disappeared completely by 3mo after the injection. These effects may be due to denervation of the medial rectus into which BTXA was injected. This denervation effect also affects the spouse muscle of medial rectus. Ultimately, the combined effect can lead to a certain degree of limitation of intraocular rotation movement of the eye, the exact cause of which is subject to further discussion.

Among the 33 AACE patients injected with BTXA in the study, 29 cases presented with orthotropic eye alignment at the final follow-up, and four patients showed recurrence of esotropia with diplopia. Recurrence was associated with the expiration of the maintenance effect of BTXA, and the duration of drug effect maintenance was also closely related to the dose and the patient's condition. The choice of BTXA re-injection or operation was provided for 4 patients with recurrence, 2 patients chose operation, and 2 patients chose secondary BTXA injection.

In conclusion, micro-injection of BTXA into the medial rectus for the treatment of AACE can reduce the esotropia deviation angle, alleviate symptoms of diplopia and reconstruct stereoacuity. The operation is relatively safe with few complications and is worthy of clinical promotion. When using BTXA injection for the treatment of AACE in clinical practice, attention should be paid to clearly defining treatment indications, correctly selecting an appropriate dose, operating with caution, and closely following up after treatment in order observe treatment effects and manage any complication in a timely manner.

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