

A Long-term Therapeutic Effect of Botulinum Toxin A for the Treatment of Strabismus

Wu Xiao

(Department of Ophthalmology, Beijing Tongren Hospital, Beijing 1000730)

Abstract

Botulinum Toxin A injection into extraocular muscle had been used to treat 53 patients of strabismus. The maximum average correction of strabismus was 40.58PD (0-110PD). The moderate and marked effects were 84.91%. Among them 43 patients have been observed for a long-term result of 6 – 36 months (mean 14.4 months). The mean correction of strabismus was 19.65PD. 21 patients received repeated injections. 12 patients obtained normal binocular single vision for 18 to 22 months eventually. The indications, the long-term therapeutic effect and the indication of repeated injection of botulinum toxin A for strabismus were discussed.

Key words: Botulinum toxin; Strabismus

Botulinum toxin A is a neurotoxin with muscular paralysis action. In 1980, Scott first applied extraocular injection of botulinum toxin A as a substitution therapy of strabismus operation and gained success, afterwards, many scholars explored application of this treatment in different types of strabismus, and indicated effectiveness of this treatment for some types of strabismus^[1-4]. Since 1991, we processed clinical studies in Chinese botulinum toxin A injection of extraocular muscles in treatment of strabismus and obtained good effects. The drug action, duration, safety and side effects were evaluated^[5]. The long-term effect of botulinum toxin A for the treatment of strabismus was observed, the indications and the indication of repeated injection were evaluated.

Material and Method

1. General Information

During March 1991 to July 1995 we cured 53 cases (58 eyes) of different types of strabismus. Age ranged from 6 – 70 years, 39 males, 14 females, the course of disease ranged from 1 month to 30 years. The strabismus type, pathogenic reason, degree of strabismus before injection were shown in Table 1, 2 and 3.

2. Method

Before injection, ophthalmology routine examinations including that of vision, anterior segment and eyeground were processed. Triple prism with cover test were

used to examine strabismus degree of 33cm and 5m and recorded. For the patients with stare disturbance, Krimsky method was used for examination. The amplitude of eye rotation was classified and recorded according to – 4(eye ball could not rotate towards a certain direction at all) to + 4(eye ball processed hyperfunction rotation towards a certain direction). For the patients whose eye ball movement was limited, stay test was processed.

Table 1 Strabismus type

Types	Cases
Paralytic esotropia	35 (40 eyes)
Paralytic exotropia	5
Concomitant esotropia	2
Concomitant exotropia	2
High myopia esotropia	2
Paralytic hyperscropia	3
Graves' Disease	3
Fixed hypotropia	1
Total	53 (58 eyes)

Table 2 Cause of disease

Cause of disease	Cases
Head injury	20
Diabetes	2
Cerebral infarction	3
Migraine	1
High myopia	2
Hyperthyroidism	3
Intrinsic	1
Unknown	21
Total	53

Table 3 Angle of squint (Triple prism angle) before and after injection

	Range	Average
Before injection	Horizontal slope	14 ~ 140
	Vertical slope	8 ~ 45
2 weeks after injection (The peak time for drug effect)	-70 ~ +70	6.92
3 months after injection (short-term)	0 ~ 75	22.66
6 months after injection (long-term)	0 ~ 75	24.74

Drug: Botulinum toxin A produced by Lanzhou Institute of Biological Products, which is a lyophilized crystalline products, each vial contained 110u or 180u, each u is the LD₅₀ for a rat, equals to 0.04ng toxin.

Injection Method: Injection of botulinum toxin A into extraocular muscle should under EMG monitoring. We used single-pole pin-like electrode and myoelectric magnifier designed by Scott, changed the myoelectric signal into sound signal. During injection, 0.5% dicaine was used in surface anesthesia, 1% adrenaline was used in reducing vasocongestion. Diluted the toxin to the required concentration (1 – 5u/0.1ml) by saline, injection volume for each piece of muscle was 0.1ml. Insert the EMG needle into the part of extraocular muscle, and insert for 15 – 20mm along muscle of orbit, told the patient to rotate eye towards direction of action of that muscle, the needle entered muscle at an angle until reaching nerve muscle junction part, at about 25mm after apodeum. Injection was performed when the high level signal was heard.

Effect Evaluation: Classified and evaluated according to the highest level of reduction of strabismus degree after injection: strabismus degree reduction \geq 10PD was defined as effective, 20PD – 40PD was defined as medium curative effective, > 40PD as apparent curative effective.

Result

89 injections were performed, among those 33 times were repeated injection. Injected muscle: internal rectus muscle for 44 eyes, external rectus muscle for 7 eyes, inferior rectus muscle for 6 eyes, superior rectus muscle for 1 eye. Dosage ranged from 1.25u – 5u (average: 2.5u).

1. Short Term Curative Effects

After 1 – 14 days of injection (average: 9.84 days) the greatest muscular paralysis effect was attained. The greatest correction after injection was 0 – 110PD, with an average of 40.58PD. There were 7 cases (13.21%) of effective, 22 cases (41.51%) of medium effective, 23 cases (43.40%) of apparent effective, 1 case (1.89%) of ineffectiveness. After 3 – 24 months (average 11.5 months) of first injection, the strabismus degree was 0 – 75PD, with an average of 22.66PD.

After the first injection, there were 16 cases of remained angle of squint \leq 10PDM, 11 cases of over correction. These 27 cases all gradually recovered to the normal position or eye position of low correction. There were 11 cases that at last obtained normal

binocular single vision function, the eye ball movement returned to normal. The other 42 cases were low correction.

2. Long Term Curative Effects

Long-term follow-up visit was processed for 43 cases (81.1%), observation period was 6 – 36 months (average 14.4 months). Examined after at least 3 months after the last injection, the average strabismus degree was 24.74PD, average corrective strabismus degree 19.65PD. Among those the strabismus degree was reduced to 0 – 15PD, the other patients were low correction, among those 6 cases returned to strabismus degree before injection, 12 cases had reduction in strabismus. For the low correction patients, 12 cases were performed the operation. 4 cases of paralysis esotropia were found with no spasm of rectus muscle during operation, function of external rectus muscle partially recovered, recession and truncation operation was done. The other 6 cases of paralytic strabismus patients processed coupling or transfer of muscle as the paralytic muscle did not recover in function. 2 cases of concomitant strabismus processed routine operations. The 6 cases that had not processed treatment plan to received repeated injection or operation therapy. After injection, the average correction of strabismus degree was 24.05PD for these 21 cases, and the average correction of strabismus degree was 13.18PD for the 11 cases of patients that were low correction but did not process repeated injection. There was no significant statistic analytic difference for these two groups of patients, but all patients had obvious objective improvement. Some paralytic strabismus patients gained partial or complete remission in function of paralytic muscle after repeated injection.

No systemic side effects occurred. Side effects of eyes were shown in Table 4. All side effects relieved to normal within 2 months.

Table Side effects of eyes

	Cases	Duration
Eyelid ptosis	19	4 – 8 weeks
Vertical strabismus	16	2 – 8 weeks
Iris dilation	2	1 – 2 weeks
Blurred vision	4	1 – 2 weeks
Conjunctival hemorrhage	2	1 – 2 weeks

Discussion

Botulinum toxin A injection into extraocular muscles was a new progress in area of strabismus. In the past 10 years, international scholars did many studies which proved

that it was a therapy that could replace surgery for some types of strabismus. The kind of disease that had been treated included the 6th and the 3rd cranial nerve palsy, low correction or over correction after strabismus operation, sensibility strabismus, strabismus after operation of detachment of retina, Graves' disease, intrinsic esotropia, etc. Since botulinum toxin A actions in a limited time, after the action decreased or disappeared, the eye position tends to low correction, most patients needed repeated injection or operation.

We performed long-term observation for different types of strabismus patients after botulinum toxin A injection, and thought that the therapy was effective except for the fixed strabismus patients. The greatest drug effect gradually decreased in 3 months, the over correction or normal position after injection gradually relived. After 6 months of injection, the drug action basically disappeared, the strabismus become stable. Patients with fusion function could maintain normal position of eye during this process. This was consistent with observation of McNeer *et al*^[6]. In this study, there were 11 cases that gained the normal position after one injection, the effect lasted for over 22 months.

Among the different types of strabismus, botulinum toxin A processed the best effect for the 6th cranial palsy patients. There were 35 paralytic esotropia patients in this study, among those 9 cases whose medical state less than 3 months gained normal position after one injection. These patients usually processed over correction in the early stage after injection, afterwards the function of paralytic muscle gradually recovered, the eye position changed to the normal position, relieved the normal binocular single vision function, and could lasted for 18 – 22 months. Patients of more than 5 months of medical state tended to fall back to original strabismus degree after disappearance of drug action. Repeated injection or operation was usually needed. After repeated injection, the strabismus degree could have different level of reduction, if the function of original paralytic muscle partially relieved, one could process the recession – truncation operation, if the function not relief, coupling was processed.

For other single-fiber extraocular palsy (medial rectus muscle, superior rectus muscle, superior obliquus muscle), the curative effect of botulinum toxin A was better, normal position was gained after one or a few number of repeated injection. However, over correction usually happened in oculomotor nerve palsy patient, it may because the functions of many paralytic extraocular muscle could not completely relief, surgical therapy was needed at last.

In patients of Graves' disease, the thickening of extraocular muscles led to limited strabismus, due to change of illness, it was difficult to predict the outcome of operation. Botulinum toxin A injection could relieve temporal diplopia, but could not eliminate pathogenic change of extraocular muscle. After disappearance of drug action, the eye position usually returned to the original oblique position. After repeated injection, the strabismus degree had a trend to decrease. Whether one could gain the normal position through multi-injection still needed further observation.

In concomitant and disuse strabismus, botulinum toxin A injection could result in normal position or over correction in the early stage, but after the drug action decreased, the eye position returned to original oblique position. Some authors thought that lack of fusion function led to unsustainable eye position. For patients who were not suitable for operation, normal position could be gradually attained after many times of repeated injection.

In this study, 74% (32 cases) of patients had low correction after one injection, among those repeated injection was performed in 21 cases. Indication of repeated injection: i) large-angle strabismus (>50PD); ii) low correction after first injection, strabismus degree > 10PD; iii) injected muscle processed contracture. Time for repeated injection: for the patients of low correction, it should be performed after 2 weeks of injection, injection dosage was adjusted according to degree of low correction, generally not exceed 5u. If the patients processed normal position or over correction after the first injection, and the eye position got back or rotation amplitude of injected muscle gradually increased from paralysis, repeated injection could be performed. For early stage of paralytic strabismus, multiple repeated injection could be performed according to changes of eye position within 6 months to maintain normal position or slight over correction. This was very essential for prevention of antagonistic muscle contracture of paralytic muscles. Since the tension of antagonistic muscles was reduced, it provided certain times for enhancement of recovery of function of paralytic muscles. We had a case of abduction nerve palsy that returned for diagnosis after 19 months of the first injection, which made the strabismus degree increased to 75PD from 40PD, obvious contracture occurred in internal rectus muscle. The other 3 cases of early stage of paralytic strabismus patients had medical state more than 6 months during procession of repeated injection, gradual recovery of function of paralytic muscle was still found, changed from -4 to -2. This change was good to both recovery of eye position or the later-on operation.

Scott reported that 40% of patients could gain the normal position after one injection, the others needed repeated injections for 2 – 7 times to gain stable results. There were

also authors thought that the effects of multiple repeated injection were better for disuse strabismus patients. In this study, 3 patients gain the normal position after repeated injection, one of those was superior rectus muscle paralysis, one was early stage of oculomotor nerve paralysis, one was early stage of bilateral abductor nerve palsy. After therapy, the function of original paralytic muscle recovered, allowed certain degree of binocular single vision function for patients, operation was avoided. Strabismus degree of other patients who processed operation after low correction decreased compared that before injection. This avoided or decreased contracture of antagonistic muscle, made the operation easier to be done. There were 2 cases of two-eyed esotropia (1 case was bilateral abductor nerve paralysis, 1 case was two-eyed limited esotropia) whose strabismus degree decreased from 105PD – 140PD to 40PD – 60PD after 2 – 3 times of injection, most function of external rectus muscle recovered, the eye position was corrected after single eye operation only.

Recently, many authors studied the clinical application of botulinum toxin A as a substitute therapy of strabismus operation, and obtained good effects. Compared with operation for a stable effect in a short period of time, the effect botulinum toxin A was not satisfactory, but for the early stage paralytic strabismus patients that could not process operation, this could be act as a way to relieve symptoms and avoid contracture. For patients with unconfirmed prognosis or not suitable for operation, botulinum toxin A could also be used. In repeated injection, gradual attainment of normal position or reduction of strabismus degree could be achieved through control of drug dosage and injection intervals, this was good for operations later-on. The eye position could be stable after 6 months injection, thus the operation should be done during that time. For paralytic strabismus patients, the operation method should be selected according to recovery condition of eye position and function of paralytic muscle, and the operation could be arranged earlier to prevent contracture of antagonistic muscles.

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