Original Article

Botulinum Toxin Injection for Treatment of Acute Traumatic Superior Oblique Muscle Palsy

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Abstract

Purpose: To evaluate the outcomes of botulinum toxin injection into the inferior oblique (IO) muscle for management of unilateral acute traumatic superior oblique (SO) palsy.

Methods: In this prospective case series, 10-20 units of botulinum toxin A (Dysport, Ipsen, Biopharm Ltd., Wrexham, UK) was injected into the ipsilateral IO muscle of 13 consecutive patients with unilateral acute traumatic SO palsy. All patients received injections within four weeks of the incident.

Results: Mean age was 29 ± 15 years and 12 (92%) subjects were male. Mean amount of hypertropia (in primary position) was decreased from 10.0 ± 3.9$^{\Delta}$ at baseline to 4.6 ± 8.9$^{\Delta}$, one month after the injection, and to 1.5 ± 2.7$^{\Delta}$ at final follow-up (P = 0.001). IO overaction improved from 2.7 ± 0.6 to 1.0 ± 1.2 and 0.6 ± 0.9 ($P \leq 0.001$), and subjective torsion from 5.3 ± 3.9 to 3.2 ± 3.4 and 1.6 ± 2.5 degrees ($P \leq 0.001$), at the same time intervals respectively. One month after the injection as well as at final follow-up, 10 (77%) patients were diplopia-free in primary and reading positions. Subgroup analysis showed that patients who recovered had less baseline hypertropia as compared to those who failed (8.3$^{\Delta}$ vs. 15.7$^{\Delta}$, respectively; P = 0.01). All patients with a favorable outcome had baseline hypertropia of 10$^{\Delta}$ or less.

Conclusion: A single injection of BTA into the IO muscle can rapidly and safely resolve symptomatic diplopia in patients with acute traumatic SO palsy, while waiting for spontaneous recovery.

Keywords: Acute; Botulinum Toxin; Dysport; Fourth Nerve Palsy; Superior Oblique Palsy; Trauma

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INTRODUCTION

Superior oblique (SO) muscle palsy, secondary to fourth cranial nerve injury, is a fairly common complication of head trauma. The chance of spontaneous recovery after acute traumatic SO palsy is less than that due to other etiologies.[1,2] Traditionally, it is recommended to follow the patients for at least 6-12 months after the injury, until the deviation has stabilized, and then decide for surgical treatment.[3] However, acute SO muscle palsy causes symptomatic diplopia, often with anomalous head posture, which may make normal activities difficult and cause psychological distress. Eye patching and prism correction are possible modalities of treatment during the observation period, usually with low patient satisfaction. The relatively long period of spontaneous recovery, the severity of bothersome diplopia, and patients' refusal to use eye patches or prisms during the observation period, prompt the need for considering an early, effective and safe intervention.

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Botulinum toxin A (BTA) injection into the ipsilateral antagonist of the paralyzed muscle causes temporary flaccid paralysis of the muscle, leading to reduced deviation, inhibition of contracture, and faster recovery of function.[4] BTA has been used successfully for management of acute traumatic third and sixth nerves palsies, with the potential to decrease the need for corrective surgery.[5,6] Studies using BTA for treatment of fourth nerve palsy are limited and most of them are comprised of heterogeneous cohorts, including both acute and chronic forms, of different etiologies.[3,7-10] In this study, we evaluate the results of BTA injection into the ipsilateral inferior oblique (IO) muscle for early management of acute traumatic SO palsy.

METHODS

In this prospective case series, 13 consecutive patients with unilateral acute traumatic SO palsy (all associated with car accidents), who were referred to a tertiary eye-care center from March 2008 through March 2012, were enrolled. The diagnosis of SO palsy was confirmed by the three-step head tilt test. Patients with other cranial nerve palsies, concomitant orbital fractures or previous strabismus surgery were excluded. All patients were diagnosed and treated within one month of the accident. Informed consent was obtained from all patients and the study was approved by the Ethics Committee at Shiraz University of Medical Sciences.

Surgical Technique

On the basis of the level of pre-injection IO muscle overaction (IOOA), 10 (for <3+ IOOA) or 20 (for ≥ 3+ IOOA) units of BTA (Dysport, Ipsen, Biopharm Ltd., Wrexham Industrial Estate, Wrexham, LL 13 9UF, UK), reconstituted in 0.1 ml of normal saline solution, was injected into the inferotemporal quadrant of the orbit. IOOA measurements were performed qualitatively, using the Atlas images provided by Rosenbaum and Santiago.[11] We prepared Dysport by dissolving the powder (500 IU) into 2.5 ml of injectable normal saline, which yielded a concentration of 20 IU/ml. For eyes that required 10 IU of Dysport, we diluted 0.1 ml of the drug suspension with 0.1 ml of additional normal saline and then injected 0.1 ml of the final suspension (10 IU/0.1 ml). The method of injection has been described previously.[3] In brief, topical anesthesia was achieved with tetracaine hydrochloride 1% (Anestocaine HCL 1%, Sina Darou, Iran). Next, with the use of a 27-gauge needle and a 1-ml insulin syringe, BTA was injected through the conjunctiva, 8-10 mm posterior to the limbus, into the muscular bulk of the ipsilateral IO muscle. The needle was held in place for about 30 seconds before being gently removed. All injections were performed by a single surgeon (MRT). No electromyography (EMG) was used to guide the operation.

Measurements

To gauge the effect of treatment, deviation was measured in primary position and in all cardinal positions, with prisms placed in front of the paretic eye, while fixating with the sound eye. Subjective torsion was measured with the red and white Double Maddox-Rod test and diplopia was assessed using a red glass test at a distance of half a meter. Ocular examinations were performed and recorded before the injection, and one, three and six months after the injection, and every six months thereafter. Recovery (or success) was defined as the absence of diplopia in primary and reading positions with hypertropia $\leq 2^{\Delta}$ at final follow-up. Those who did not recover six months after the injection were scheduled for strabismus surgery.

Statistical Analysis

All statistical analyses were performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Friedman test and the Wilcoxon Signed-Ranks test were used for comparing pre- and post-injection data. For subgroup analysis, the Fisher's exact and Mann-Whitney U-tests were used to compare patients who recovered with those who did not. P values < 0.05 were considered as statistically significant.

RESULTS

Mean age of the patients was 29 ± 15 (range 16 to 74) years and 12 (92%) were male. In eight patients (62%) the right eye was involved. The cause of trauma was motor vehicle accidents in all patients. Every patient presented with binocular diplopia in primary and reading positions.

Mean IOOA, hypertropia in primary gaze, and subjective torsion were significantly decreased one month after the injection and at final follow-up, as compared to baseline measurements [Table 1]. Since data at three months, six months and at final follow-up were not statistically different, only final follow-up data are presented. Overall, 10 (77%) patients recovered one month after the injection. At final follow-up, success rate was not changed; those who were diplopia-free at one month remained diplopia-free and those who failed at one month remained failed at final follow-up. Mean follow-up period for recovered patients was 20.4 ± 10.3 (median, 21; range: 6-36) months. Three (23%) patients who did not recover after six months of follow-up finally underwent inferior oblique (IO) myectomy, which was successful in all cases. Pre- and post-injection data is presented in Table 2.

Subgroup analysis showed that recovered patients had less mean baseline hypertropia as compared to subjects who failed to respond (8.3$^{\Delta}$ vs. 15.7$^{\Delta}$, respectively; P = 0.01; Table 3). Baseline torsion and IOOA also revealed

Table 1. Eye deviation measurements at baseline, 1 month and at final FU examination after BTA injection into the inferior oblique muscle for unilateral acute traumatic superior oblique palsy

	Baseline			1 month			Last FU			*P**	Pair-wise comparison†
	Mean (median)	SD	Range	Mean (median)	SD	Range	Mean (median)	SD	Range		
Hypertropia (Δ)	10.0 (9)	3.9	6-20	4.6 (0)	8.9	0-24	1.5 (0)	2.7	0-8	0.001	P_a: 0.006 P_b: 0.001 P_c: 0.144
IOOA	2.7 (3)	0.6	2-4	1 (1)	1.2	0-4	0.6 (0)	0.9	0-3	<0.001	P_a: 0.002 P_b: 0.001 P_c: 0.059
Torsion (degrees)	5.3 (6)	3.9	0-10	3.2 (4)	3.4	0-9	1.6 (0)	2.5	0-8	<0.001	P_a: 0.017 P_b: 0.007 P_c: 0.017

*Friedman test; †Wilcoxon signed ranks test. P_a, baseline versus 1 month; P_b, baseline versus last FU; P_c, 1 month versus last FU; Δ, prism diopter(s); BTA, botulinum toxin A; FU, follow-up; IOOA, inferior oblique muscle overaction; SD, standard deviation; *P*, probability

Table 2. Patients' characteristics and eye deviation measurements before and at final FU after BTA injection into inferior oblique muscle for unilateral acute traumatic superior oblique palsy

Case	Sex	Age, years	BTA, unit	FU, month (s)	Hypertropia, Δ			IOOA			Torsion, degree			Success‡
					Baseline	1 month	Last FU	Baseline	1 month	Last FU	Baseline	1 month	Last FU	
1	Male	16	10	36	10	0*	0	2	0	0	6	0	0	Yes
2	Male	22	20	6	12	16†	4	3	2	1	8	8	3	No
3	Male	28	10	36	8	0	0	2	0	0	0	0	0	Yes
4	Male	30	20	6	15	20†	6	3	2	1	8	6	4	No
5	Male	18	20	6	20	24†	8	4	4	3	9	9	8	No
6	Male	20	20	24	8	0	0	3	1	0	0	0	0	Yes
7	Male	30	20	24	9	0	0	3	1	1	6	4	2	Yes
8	Female	35	10	24	10	0	0	2	1	1	6	0	0	Yes
9	Male	25	20	18	8	0	2	3	0	1	8	4	0	Yes
10	Male	26	10	12	6	0	0	2	0	0	0	0	0	Yes
11	Male	18	20	12	10	0	0	3	1	0	8	4	0	Yes
12	Male	74	10	12	6	0	0	2	0	0	0	0	0	Yes
13	Male	36	20	6	8	0	0	3	1	0	10	6	4	Yes

*Less than 2 diopters of deviation was regarded as no significant deviation, and these eyes were regarded as zero in data analysis; †Showed transient hypertropia after injection which resolved later; ‡Cases with success or failure at 1 month showed exactly the same outcome at final FU. Δ, prism diopter(s); BTA, botulinum toxin A; FU, follow-up; IOOA, inferior oblique muscle overaction

Table 3. Comparison of baseline characteristics grouped by outcome

	Recovered	Failed	*P*
Number	10	3	-
Gender, male/female	3/0	9/1	1.0
Age* (years)	31 (27)±17	23 (22)±6	0.498
Hypertropia* (Δ)	8.3 (8.0)±1.5	15.7 (15.0)±4.0	0.010
IOOA*	2.5 (2.5)±0.5	3.3 (3.0)±0.6	0.057
Torsion* (degree)	4.4 (6.0)±4.0	8.3 (8.0)±0.6	0.080

*Data are presented as mean (median)±SD. Δ, prism diopter(s); IOOA, inferior oblique muscle overaction; SD, standard deviation

a non-significant trend toward lower values in recovered patients. There was no significant difference in age and sex between the subgroups [Table 3]. Mean post-injection change (baseline minus final follow-up) in hypertropia was 8.5 ± 1.8Δ (median, 8.0; range: 6-12Δ). Post-injection changes in ocular deviation, grouped by outcomes of treatment, are presented in Table 4. Linear regression analysis showed that baseline hypertropia was the only independent factor associated with post-injection change in hypertropia (r = 0.77; *P* = 0.02; Figure 1). Other factors, including age, sex, baseline IOOA, baseline torsion, and amount of BTA injection did not show any significant association with the post-injection change in hypertropia.

No major complications (such as globe perforation) occurred during the procedure. Minor complications comprised of transient ptosis in four patients, transient excessive hypertropia secondary to inferior rectus paresis in three cases (all of whom received 20 units of Dysport, and eventually failed to respond, Table 2), and subconjunctival hemorrhage in five patients.

Table 4. Post-injection changes (baseline - last follow-up) in ocular deviation grouped by outcome

	Recovered	Failed	*P*
Hypertropia* (Δ)	8.1 (8.0)±1.7	9.7 (9.0)±2.1	0.298
IOOA*	2.2 (2.0)±0.6	1.7 (2.0)±0.6	0.287
Torsion* (degree)	3.8 (5.0)±3.5	3.3 (4.0)±2.1	0.811

*Data are presented as mean (median)±SD. Δ, prism diopter(s); IOOA, inferior oblique muscle overaction; SD, standard deviation

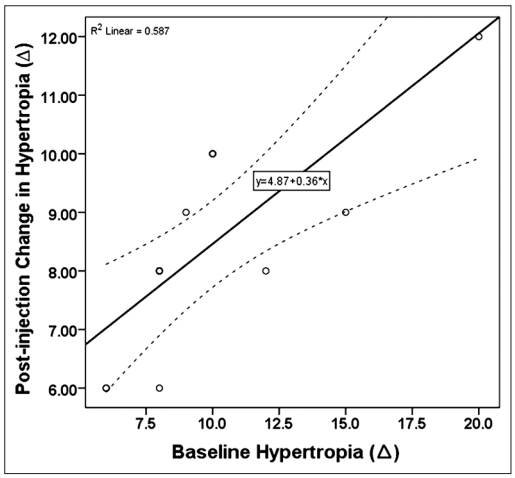

Figure 1. Scatter plot and linear regression analysis showing the association between post-injection (baseline - last follow-up) change in hypertropia against baseline hypertropia in cases with unilateral acute traumatic superior oblique palsy treated with botulinum toxin A. The solid line is the fit line and dotted lines show 95% confidence intervals. Δ, prism diopter.

DISCUSSION

The results of the present study show that in patients with unilateral acute traumatic SO palsy, a single injection of BTA into the IO muscle rapidly led to a more normal binocular status in all patients. Intervention was also successful in achieving complete resolution of diplopia in 77% of the patients at the one month, which persisted until final follow-up. All patients with a successful outcome had baseline hypertropia of 10^{Δ} or less. All three patients in whom diplopia did not resolve had baseline hypertropia of $\geq 12^{\Delta}$. Although the absolute amount of post-injection change in hypertropia showed a direct association with baseline hypertropia [Figure 1], the probability to gain post-injection residual hypertropia of $\leq 2^{\Delta}$ (which offered diplopia-free gaze in primary and reading positions) diminished, as baseline hypertropia increased. According to our results, cases with baseline hypertropia of $\leq 10^{\Delta}$ are more likely to attain a favorable outcome after BTA injection, when compared with more severe cases. In addition, all cases that showed a favorable outcome at one month, maintained the outcome at the last examination, and those who did not respond to BTA injection did not recover thereafter. The possible prognostic value of BTA injection for determining patients who will or will not recover later through the natural course of the disease must be further investigated.

Bagheri et al[3] reported on BTA injection into the IO muscle for a heterogeneous cohort of patients with SO palsy. Of the 16 patients enrolled, 13 were traumatic, 14 were unilateral, and most were chronic. After six months, a good outcome was reported in 10 cases (62.5%); they observed that more chronic disease was associated with less likelihood of a good outcome. In line with Bagheri et al[3] our study showed that the chance of a good outcome diminished with an increased magnitude of baseline hypertropia. According to their results, mean (SD) hypertropia decreased from $6.4\ (4.9)^{\Delta}$ to $1.9\ (4.5)^{\Delta}$ six months after treatment.[3] In our study, mean hypertropia decreased from $10\ (3.9)^{\Delta}$ to $1.5\ (2.7)^{\Delta}$. The greater magnitude of reduction in our study could be attributed to the more acute nature of palsy in our patients, which probably made them more susceptible to the injection, and also lower baseline hypertropia in the study by Bagheri et al[3]

Some previous studies used an EMG guide during BTA injection into the IO muscle.[7-9] However, the technique is complex and in some instances the IO muscle cannot be localized with EMG.[8,9] It has been hypothesized that injection into the perimuscular connective tissue is sufficient to achieve adequate paralysis and direct injection into the muscle belly is not imperative.[12] Similar to Bagheri et al[3] we did not use an EMG guide, however the desired paralytic effect was achieved in every case; this method is more rapid and easy to perform.

Injecting BTA into or around the IO muscle has the potential of spreading into the lateral, or particularly the inferior, rectus muscles. Previous studies showed that the risk is increased with higher doses of BTA.[3,9] Similar to Bagheri et al[3] we observed no inferior rectus paresis with 10 units of Dysport. The three cases in our study (23%) and the two (11%) in the Bagheri et al study,[3] with transient inferior rectus paresis, had received 20 units of Dysport. Buonsanti et al[9] reported that in five cases (27%) the toxin spread to the lateral and/or inferior rectus muscles; the risk reached 50% by injecting 10 units of Botox (equal to 40 units of Dysport). On the whole, to achieve adequate IO paresis and minimize complications, experts recommend 2.5-5 units of Botox (equal to 10-20 units of Dysport).[3,9]

The major drawback of the present study is limited sample size, precluding more valid or precise conclusions about the effect of baseline characteristics on outcomes of injection. Moreover, our study lacked a control group. Future randomized clinical trials could explore the effect of BTA, as compared to observation or standard treatments. The power of the current study was homogeneity of patients, a consistent therapeutic approach and early intervention, which allowed drawing an explicit conclusion from the results.

In conclusion, the results of the present study suggest that a single injection of BTA into the IO muscle can rapidly and safely resolve symptomatic diplopia in patients with acute traumatic SO palsy, while waiting for spontaneous recovery. The procedure is most effective for patients with baseline hypertropia of 10^{Δ} or less. The value of multiple injections must be investigated in future studies.

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Conflicts of Interest

There are no conflicts of interest.

REFERENCES

1. Tiffin PA, MacEwen CJ, Craig EA, Clayton G. Acquired palsy of the oculomotor, trochlear and abducens nerves. *Eye* (*Lond*) 1996;10:377-384.
2. Rush JA, Younge BR. Paralysis of cranial nerves III, IV, and VI. Cause and prognosis in 1,000 cases. *Arch Ophthalmol* 1981;99:76-79.
3. Bagheri A, Eshaghi M. Botulinum toxin injection of the inferior oblique muscle for the treatment of superior oblique muscle palsy. *J AAPOS* 2006;10:385-388.
4. Crouch ER. Use of botulinum toxin in strabismus. *Curr Opin Ophthalmol* 2006;17:435-440.
5. Talebnejad MR, Sharifi M, Nowroozzadeh MH. The role of Botulinum toxin in management of acute traumatic third-nerve palsy. *J AAPOS* 2008;12:510-513.
6. Hung HL, Kao LY, Sun MH. Botulinum toxin treatment for acute traumatic complete sixth nerve palsy. *Eye* (*Lond*) 2005;19:337-341.
7. Merino P, Gómez de Liaño P, García C, Bartolomé G, Rodríguez C, De Juan L. Bilateral superior oblique palsy and botulinum toxin. *Arch Soc Esp Oftalmol* 2004;79:119-123.
8. Lozano-Pratt A, Estanol B. Treatment of acute paralysis of the fourth cranial never by botulinum toxin A chemodenervation. *Binocul Vis Strabismus Q* 1994;9:155-158.
9. Buonsanti J, Sanchez-Covisa M, Scarfone H, Lynch J. Botulium toxin chemodenervation of the inferior oblique muscle for chronic and acute IV nerve palsies: Results in 15 cases. *Binocul Vis Strabismus Q* 1996;11:119-124.
10. Garnham L, Lawson JM, O'Neill D, Lee JP. Botulinum toxin in fourth nerve palsies. *Aust N Z J Ophthalmol* 1997;25:31-35.
11. Rosenbaum AL, Santiago AP. Clinical Strabismus Management: Principles and Surgical Techniques. Philadelphia, PA: W.B. Saunders; 1999. p. 17.
12. Kao LY, Chao AN. Subtenon injection of botulinum toxin for treatment of traumatic sixth nerve palsy. *J Pediatr Ophthalmol Strabismus* 2003;40:27-30.