Botulinum Toxin Treatment of the Sixth Nerve Palsy: An Experience of 5-Year Duration in Thailand

WANICHA CHUENKONGKAEW, M.D.*,
DHAIVADEE DULAYAJINDA, M.D.*,
RASRI DEETAE, B.N.S.*

Abstract

Forty-five patients (48 eyes) with sixth nerve palsy were treated with botulinum toxin injection to antagonist medial rectus muscle at Siriraj Hospital from October 1995 to September 2000. The common causes of palsy were ischemia, trauma and inflammation. Thirty-eight patients (group I) had an interval to treatment of less than 24 weeks (average, 8.7 weeks) and seven patients (group II), longer than 24 weeks. The mean pre-injection esodeviation and extent of abduction in group I were 28.1 prism diopters (PD) and 28.4 per cent, and in group II were 38 PD and 8.1 per cent respectively. After a mean follow-up of 12.2 months, twenty-seven (71.1%) patients in group I recovered completely after the first injection and three (7.9%), after the second injection with a mean interval to recovery of 8.1 weeks. One (14.3%) of 7 patients of group II obtained complete recovery without fusion. Twenty-six (83.9%) of 31 patients with complete resolution achieved binocular function. We conclude that botulinum toxin treatment is a safe and effective alternative to traditional surgery of acute onset sixth nerve palsy.

Key word : Botulinum Toxin Injection, Abducens Palsy

CHUENKONGKAEW W, DULAYAJINDA D, DEETAE R
J Med Assoc Thai 2001; 84: 171-176

Botulinum toxin which is a presynaptic neuromuscular blocking agent resulting in temporary paralysis of injected muscle has been considered to be effective in the treatment of strabismus especially from sixth nerve palsy since 1985 (1-4). It has been postulated that botulinum toxin may prevent contractures of the antagonist medial rectus muscle, allowing restoration of

* Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

normal ocular alignment after the return of lateral rectus function. However, some articles have recently documented that botulinum toxin is not beneficial in acute or long-standing sixth nerve palsy[5-7].

Since we reported botulinum toxin treatments in 12 patients who developed unilateral or bilateral sixth nerve palsy in 1997,[8] we continued the treatment in another 35 patients in order to determine the clinical response of botulinum toxin injection in sixth nerve palsy with a mean follow-up period of 12.2 months from last injection.

MATERIAL AND METHOD

Botulinum toxin injections were given under written informed consent in 47 patients (51 eyes) with unilateral and bilateral sixth cranial nerve palsy in Siriraj Hospital between October 1995 and September 2000. Two patients were excluded due to loss of follow-up data and ambiguous diagnosis in a patient with bilateral palsy. Data collected from the patients included age, sex, causes of sixth nerve palsy, interval from palsy to injection, pre- and post- injection of angle of deviation in primary position by red glass test with the deviating eye being the fixating eye or Krimsky method in case of poor vision, ability in abduction of the affected eye to rotate from midline to field of gaze, intraocular pressure, palpebral fissure distance, marginal reflex distance and post-injection stereopsis by Titmus fly test. Complete recovery was defined as no residual esotropia and absence of abduction deficit.

Method of botulinum toxin injection

Dosage of injected botulinum toxin depended on the angle of deviation which was shown as follows: a dosage of 2.5 units if the deviating angle was less than 20 PD, a dosage of 5.0 units if the deviating angle was between 20 and 50 PD and a dosage of 7.5 units if the deviating angle was larger than 50 PD.

Technique of injection

The topical anesthetic eye drop was applied to the affected eye once per minute for 10 minutes. In addition, one drop of 2.5 per cent phenylephrine eye drop was also instilled 10 minutes before injection to reduce vascularity of tissue and allow better visualization of the underlying muscle. A tetracaine-soaked cotton-tipped swab was placed over the conjunctiva at the injection site just before the procedure. The injection was performed by using a 1 ml tuberculin syringe with a Teflon-coated monopolar needle and electromyographic (EMG) guidance to confirm the needle location. The neutral electrode of EMG was placed at the patient's forehead, whereas, the active electrode was connected to the needle. In order to penetrate at the neuromuscular junctions of the medial rectus muscle, the patient was initially instructed to look in the opposite field to the injected muscle until an EMG signal was heard. Then the patient was instructed to look into the field of action of the muscle, so the noise would be louder. To avoid puncturing the globe, the needle was placed at an angle of 90 degrees into the muscle and away from the eye. Finally, botulinum toxin was injected when the high level EMG signal was heard followed by withdrawal of the needle, and the patient immediately was raised to the sitting position to prevent ptosis. Upon finishing the procedure, steroid eye ointment with eye patching was applied to the injected eye. The patch was removed the following day and the patient was reexamined 3 and 7 days and once a month after injection until the esodeviation remained constant or disappeared, and was reevaluated every sixth months. In case of a return of esodeviation or diplopia, another injection was given.

RESULTS

A total of 70 botulinum toxin injections were given to 42 patients (92.9%) with unilateral sixth nerve palsy and 3 patients (7.1%) with bilateral sixth nerve palsy. Of the 45 patients, 27 patients (60%) were male and 18 patients (40%) were female. Their ages ranged from 15 to 75 years old (average, 42.7 years old). The causes of sixth nerve palsy are shown in Table 1.

The most common cause of unilateral nerve palsy was ischemia the underlying diseases being hyperlipidemia (9 patients), diabetes mellitus (8 patients), and hypertension (4 patients). Ischemia (2 patients) and trauma (1 patient) were also found to be the etiologies in bilateral sixth nerve palsy.

The characteristics of the patients are shown in Table 2. Of the 45 patients, 38 patients

Table 1. The causes of the sixth cranial nerve palsy.

Cause	Numbers of patients	%
Ischemia	18	40
Trauma	14	31.1
Inflammation	6	13.3
Nasopharyngeal carcinoma metastasis	2	4.4
Nerve compression from aneurysm	1	2.2
Post embolization of carotid-cavernous fistula	1	2.2
Undetermined	3	6.7
Total	45	100

(40 eyes) (84.4%) who received botulinum toxin injection within 24 weeks after onset were classified in group I and 7 patients (8 eyes) (15.6%) given treatment longer than the 24-week period after the palsy were in group II of whom 2 patients with interval to injections of 2 and 13 years had previously undergone the conventional muscle surgical procedure. The mean interval time from palsy to treatmant in group I was 8.7 weeks (ranging from 2-24 weeks) and in group II which did not include a patient who had long-standing onset, and the mean interval to treatment was 41.7 weeks (ranging from 28-104 weeks).

Pre-injection data

The mean angle of esodeviation and extent in abduction of the affected eye were 28.1 PD and 28.4 per cent in group I and 38 PD and 8.1 per cent in group II respectively.

Post-injection data

Of the 38 patients in group I, 27 patients (71.1%) completely recovered after the first injection with mean interval to recovery of a 7.9-week period. Repeated injections which varied from 2 to 5 injections (average 2.5 injections) were given in 8 patients in group I, of whom there were 3 patients with minimal residual esotropia, 2 patients with recurrence in ipsilateral eye finally obtained complete recovery and one patient later required surgical correction to maintain cosmetic alignment. Of 8 patients (21.1%) in group I whose palsies did not recover or partially recovered, one was bilateral palsy, four patients whose interval to palsy longer than 12 weeks and large pre-injected angle of esodeviation had total abduction deficit caused by severe trauma and three partially recovered with 15 PD residual esotropia but full rotation. All except one in group II had partial resolution despite multiple injections, 2 patients each with bilateral palsy, long-standing palsy (onset of more than 2 years) and unilateral palsy caused by nasopharyngeal carcinoma. Of the 31 patients who were diplopia-free after the treatment, twenty-six (83.9%) regained binocular function, whereas, the remaining 5 patients (16.1%) obtained only normal ocular alignment but no stereopsis.

The most common complication of botulinum toxin injection was ptosis which occurred in 20 patients (55.6%) and recovery was within a mean of 4.9 weeks (Table 3). Hypertropia and bleeding were also found to be common complications of injection. These symptoms disappeared within 6 weeks after the injection.

DISCUSSION

Botulinum toxin has been widely reported in the management of acute sixth nerve palsy and occasionally advocated in chronic sixth nerve palsy[1-3,9,10]. The result of injection is not to alleviate the disturbing esotropia by paralyzing

Table 2. Characteristics of the patients in group I and II.

Characteristics	Group I patient	Group II patient
Number of patients (eyes)	38 (40)	7 (8)
Interval to treatment in weeks (average)	2-24 (8.7)	28-104 (41.7)*
Angle of deviation in prismdiopters (average)	10-70 (28.1)	10-50 (38)
% of ability in abduction of deviating eye (average)	0-90 (28.4)	0-30 (8.1)
Number of patients with complete recovery after injection (eyes)	30 (31)	1 (1)
Interval to complete recovery in weeks (average)	1-34 (8.1)	20

* not included a patient who had interval to treatment of 13 years

Table 3. Complication of botulinum toxin injection.

Complication (number of patients)	Current study (45)	Scott et al[1] (32)	Metz et al[3] (21)	Biglan et al[5] (149)
Ptosis	20	5	10	38
Hypertropia	6	1	9	27
Bleeding	4	1	-	5
Head posture	-	-	-	6
Decreased vision	-	-	-	2
Headache	1	-	-	1
Over-correction	-	5	-	-
Abnormal sensation	-	1	-	-
Increased intra-ocular pressure	5	-	-	-

the ipsilateral medial rectus muscle but to restore stereopsis by allowing the eye to abduct passively, enabling a small area of binocularity to be obtained. In addition, if the paralyzed medial and lateral rectus muscles recover at the same time and rate, the area of single binocular vision will be enlarged. Although spontaneous resolution generally occurs in 30-50 per cent of patients with sixth nerve palsy especially a higher rate in acute traumatic palsy,[11-14] the patients may regain only normal cosmetical ocular alignment but not stereopsis because contracture of the unopposed medial rectus muscle can lead to persistent residual esotropia despite a return of lateral rectus muscle function.

In our study, 79 per cent of patients who had onset of palsy within 24 weeks compared with14.3 per cent of patients with long-standing palsy were successfully treated by botulinum toxin and mostly recovered within 8 weeks after the injection, though some required more than one injection. As documented in many reports, botulinum toxin was of limited value in patients with chronic sixth nerve palsy and not as effective as surgical treatment[4,5]. Of the sixth nerve palsy patients displaying complete recovery with binocular function achievement after botulinum toxin treatment, 83.9 per cent did so in this study. However, our patients with long-standing palsies had acceptable outcome but no fusion was achieved. This may result from the extent of weakness of lateral rectus muscle in chronic palsy which is usually complete producing stiffness in elasticity of the two horizontal muscles and leads to a lower rate of recovery after six months.

The etiology and laterality of palsy were suggested as the other factors that influenced the rate of recovery. The unilateral sixth nerve palsy patients caused by ischemia, trauma and inflammation which were the common etiologies in this study had remarkable improvement, whereas, patients with nasopharyngeal carcinoma and bilateral palsy experienced very little improvement.

Ptosis, which has been documented to be the most common complication of botulinum toxin injection occurred in 55.6 per cent and spontaneously resolved within a mean interval of 4.9 weeks after injection[1,3,5]. Moreover, we found some patients with reversible increased intra-ocular pressure after injection, which has never before been demonstrated in other studies.

Botulinum toxin is determined to be an effective and a safe treatment particularly in acute onset sixth nerve palsy because of its benefit both in cosmetic ocular alignment and single binocular function restoration but not appearing to facilitate recovery in chronic palsy. However, injection may be considered to be an alternative treatment in chronic palsy patients who are contraindicated for conventional surgery.

ACKNOWLEDGEMENT

The authors wish to thank Professor Niphon Poungvarin, Head of the Neurology Unit, Department of Medicine, Siriraj Hospital for his support in this study.

(Received for publication on October 31, 2000)

REFERENCES

1. Scott AB, Kraft SP. Botulinum toxin injection in the management of lateral rectus paresis. Ophthalmology 1985; 92: 676-83.
2. Elston JS, Lee JP. Paralytic strabismus: the role of botulinum toxin. Br J Ophthalmol 1985; 69: 891-6.
3. Metz HS, Dickey CF. Treatment of unilateral acute sixth-nerve palsy with botulinum toxin. Am J Ophthalmol 1991; 112 : 381-4.
4. Repka MX, Lam GC, Morrison NA. The efficacy of botulinum toxin A for the treatment of complete and partially recovered chronic sixth nerve palsy. J Pediatr Ophthalmol Strabismus 1994; 31: 79-83.
5. Biglan AW, Burnstine RA, Rogers GL, Saunders RA. Management of strabismus with botulinum toxin A toxin. Ophthalmology 1989; 96: 935-43.
6. Filzsimons R, Lee J, Elston J. The role of botulinum toxin in the management of sixth nerve palsy. Eye 1989; 3: 391-400.
7. Lee J, Harris S, Cohen J, et al. Results of a prospective randomized trial unilateral sixth nerve palsy. J Pediatr Ophthalmol Strabismus 1994; 31: 283-6.
8. Chuenkongkaew W, Dulayajinda D. Botulinum toxin treatment of sixth cranial nerve palsy. Siriraj Hosp Gaz 1997; 49: 339-44.
9. Wagner RS, Frohman LP. Long-term results: botulinum for sixth nerve palsy. J Pediatr Ophthalmol Strabismus 1989; 26: 106-8.
10. Murray AND. Early and late botulinum toxin treatment of acute sixth nerve palsy. Aust N Z J Ophthalmol 1989; 17: 239-45.
11. Rush JA, Younge BR. Paralysis of cranial nerve III, IV and VI. Causes and prognosis in 1,000 cases. Arch Ophthalmol 1981; 99: 76-9.
12. Metz HS, Mazow M. Botulinum toxin treatment of acute sixth and third nerve palsy. Graefes Arch Clin Exp Ophthalmol 1988; 226: 141.
13. Holmes JM, Droste PJ, Beck RW. The natural history of acute traumatic sixth nerve palsy or paresis. J AAPOS 1998; 2: 265-8.
14. Holmes JM, Beck RW, Kip KE, et al. Botulinum toxin treatment *versus* conservative treatment in acute traumatic sixth nerve palsy or paresis. J AAPOS 2000; 4: 145-9.

การศึกษาผลการรักษาภาวะตาเขเนื่องจากอัมพาตของเส้นประสาทสมองเส้นที่ 6 โดยการฉีด Botulinum Toxin ในประเทศไทยประสบการณ์ 5 ปี

วณิชา ชื่นกองแก้ว, พ.บ., ไธวดี ดุลยจินดา, พ.บ.*, ราศี ดีแท้, พย.บ.**

รายงานการศึกษาการฉีด botulinum toxin เข้ากล้ามเนื้อ medial rectus ในผู้ป่วยตาเขเนื่องจากอัมพาตของเส้นประสาทสมองเส้นที่ 6 ที่มารับการรักษาที่โรงพยาบาลศิริราช ตั้งแต่เดือนตุลาคม 2538 ถึงเดือนกันยายน 2543 จำนวน 45 ราย ซึ่งสาเหตุส่วนใหญ่เกิดจากภาวะกล้ามเนื้อตาขาดเลือดไปเลี้ยง จากอุบัติเหตุ และจากการอักเสบของกล้ามเนื้อตา ผลการศึกษาพบผู้ป่วยกลุ่มที่ 1 ซึ่งได้รับการฉีดยาภายในระยะเวลา 24 สัปดาห์ (ระยะเวลาเฉลี่ย 8.7 สัปดาห์) หลังเกิดอาการตาเขจำนวน 38 ราย และผู้ป่วยกลุ่มที่ 2 ได้รับการฉีดยาภายหลังระยะเวลา 24 สัปดาห์ หลังเกิดอาการตาเขจำนวน 7 ราย ค่าเฉลี่ยของปริมาณมุมเขในท่ามองตรงและความสามารถในการทำงานของกล้ามเนื้อ lateral rectus ก่อนการฉีดยาในผู้ป่วยกลุ่มที่ 1 เท่ากับ 28.1 ปริซึมไดออปเตอร์ และร้อยละ 28.4 และในผู้ป่วยกลุ่มที่ 2 เท่ากับ 38 ปริซึมไดออปเตอร์ และร้อยละ 8.1 ภายหลังการติดตามผลการรักษาเป็นระยะเวลาเฉลี่ย 12.2 เดือน ในผู้ป่วยกลุ่มที่ 1 ไม่มีอาการตาเขเหลืออยู่ภายหลังการฉีดยาครั้งแรกจำนวน 27 ราย (ร้อยละ 71.1) และภายหลังการฉีดยาครั้งที่สองจำนวน 3 ราย (ร้อยละ 7.9) ซึ่งพบว่าผู้ป่วยทุกรายมี single binocular vision กลับเป็นปกติ ในขณะที่ผู้ป่วยในกลุ่มที่ 2 ไม่มีอาการตาเขเหลืออยู่แต่ไม่มี single binocular vision จำนวน 1 ราย (ร้อยละ 14.3) ดังนั้นการรักษาภาวะตาเขเนื่องจากอัมพาตของเส้นประสาทสมองเส้นที่ 6 โดยการฉีด botulinum toxin จึงเป็นวิธีการรักษาที่มีประสิทธิภาพในผู้ป่วยที่มีอาการอย่างเฉียบพลันมากกว่าผู้ป่วยที่มีอาการเรื้อรัง

คำสำคัญ : ตาเขเนื่องจากอัมพาตของเส้นประสาทสมองเส้นที่ 6, การฉีด botulinum toxin

วณิชา ชื่นกองแก้ว, ไธวดี ดุลยจินดา, ราศี ดีแท้
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 171-176

* ภาควิชาจักษุวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพฯ 10700