



## ORIGINAL ARTICLE

# Botulinum toxin for treatment of restrictive strabismus<sup>☆</sup>



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### KEYWORDS

Acquired restrictive strabismus;  
Botulinum toxin;  
Graves ophthalmopathy;  
Myopic acquired strabismus;  
Strabismus secondary to cataract surgery

### Abstract

**Purpose:** To study the types of acquired restrictive strabismus treated in a tertiary hospital and the outcome of treatment with botulinum toxin.

**Methods:** We performed a 10-year retrospective study of patients with restrictive strabismus aged  $\geq 18$  years who were treated with botulinum toxin. Treatment was considered successful if the final vertical deviation was  $\leq 5$  PD, horizontal deviation  $\leq 10$  PD, with no head turn or diplopia.

**Results:** We included 27 cases (mean age, 61.9 years). Horizontal strabismus was diagnosed in 11.1%, vertical in 51.9%, and mixed in 37%. Strabismus was secondary to cataract surgery in 6 cases, high myopia in 6, orbital fractures in 5, retinal surgery in 5, Graves ophthalmopathy in 4, and repair of conjunctival injury in 1 case. Diplopia was diagnosed in all patients, head turn in 33.3%. The initial deviation was 14 PD (range, 2–40), the mean number of injections per patient was 1.6 (range, 1–3), and the mean dose was 9.5 IU (range, 2.5–22.5). At the end of follow-up, diplopia was recorded in 59.3%, head turn in 18.5%, surgical treatment in 51.9%, and need for prism glasses in 14.8%. Outcome was successful in 37% of patients (4 high myopia, 3 orbital fractures, 2 post-surgical retinal detachment, and 1 post-cataract surgery). Mean follow-up was  $3 \pm 1.8$  years.

**Conclusion:** Vertical deviation was observed in half of the sample. The most frequent deviation was secondary to cataract surgery and high myopia. Treatment with botulinum toxin was successful in one-third of the patients at the end of follow-up.

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**PALABRAS CLAVE**

Estrabismo restrictivo adquirido;  
Toxina botulínica;  
Oftalmopatía de Graves;  
Estrabismo miópico adquirido;  
Estrabismo secundario a cirugía de cataratas

**Botox y estrabismo restrictivo****Resumen**

**Objetivo:** Estudiar los tipos de estrabismo restrictivo adquirido tratados en un hospital terciario, y los resultados del tratamiento utilizando toxina botulínica.

**Métodos:** Realizamos un estudio retrospectivo de diez años en pacientes con estrabismo restrictivo y edades  $\geq 18$  años, a quienes se trató con toxina botulínica. El tratamiento se consideró exitoso cuando la desviación vertical final fue  $\leq 5$  PD, la desviación horizontal  $\leq 10$  PD, y no se produjo torsión ni diplopía.

**Resultados:** Incluimos 27 casos (edad media, 61,9 años). Se diagnosticó estrabismo horizontal en el 11,1% de los casos, vertical en el 51,9%, y mixto en el 37%. El estrabismo fue secundario a: cirugía de cataratas en 6 casos, miopía magna en 6, fracturas orbitales 5, cirugía de la retina en 5, oftalmopatía de Graves en 4, y reparación de lesiones conjuntivales en 1 caso. Se diagnosticó diplopía en todos los pacientes, y tortícolis en el 33,3%. La desviación inicial fue de 14 PD (rango, 2–40), el número medio de inyecciones por paciente fue de 1,6 (rango, 1-3), y la dosis media de 9,5 IU (rango, 2,5-22,5). Al final del seguimiento, se registró diplopía en el 59,3% de los casos, tortícolis en el 18,5%, tratamiento quirúrgico en el 51,9%, y necesidad de gafas prismadas en el 14,8%. El resultado fue exitoso en el 37% de los pacientes (4 miopes magnos, 3 fracturas orbitaria, 2 post-cirugía de desprendimiento de retina, y 1 post-cirugía de cataratas). El seguimiento medio fue de  $3 \pm 1,8$  años.

**Conclusión:** Se observó desviación vertical en la mitad de la muestra. La desviación más frecuente fue secundaria a la cirugía de cataratas y a miopía magna. El tratamiento con toxina botulínica fue exitoso en una tercera parte de los pacientes al finalizar el seguimiento.

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**Introduction**

Botulinum toxin was first reported as an alternative to strabismus surgery in 1980 by Scott.<sup>1</sup> It can be used to treat acquired restrictive strabismus and proved to be successful or at least acceptable for treatment of thyroid strabismus.<sup>2</sup>

Most data in the literature are from isolated case reports or small samples describing the effect of treatment with botulinum toxin on acquired restrictive strabismus.<sup>3,4</sup> The effect of botulinum toxin has been reported to be diminished in this type of strabismus,<sup>2</sup> with a 2-month duration of effect and the need for repeat injections to achieve results similar to those achieved in comitant strabismus and oculomotor palsy.<sup>3</sup> Most patients need surgery after administration of botulinum toxin.<sup>2</sup> Results for thyroid strabismus have been good, with a 75% decrease in the initial deviation and a favorable outcome in 45.45% of cases.<sup>3,5</sup> Botulinum toxin relaxes the inflammatory spasm that is characteristic of the acute phase of the condition, although its effect on the muscular fibrosis and contracture that appear during the clinical course is minimal.<sup>5</sup> Restrictive strabismus secondary to orbital disorders seems to respond well to botulinum toxin, especially in inflammatory conditions or myositis, although treatment has little effect in orbital fractures. The effect of botulinum toxin is independent of the initial deviation.<sup>6</sup> Other types of restrictive strabismus secondary to retinal detachment surgery, cataract surgery, and strabismus surgery have been treated with botulinum toxin, with variable results.<sup>7–10</sup>

The benefit of botulinum toxin in restrictive strabismus is open to debate. Therapeutic response is associated with

the type of deviation (vertical or horizontal), the extent of deviation, early treatment, age, and type of restrictive strabismus. The objectives of this study were to describe the types of acquired restrictive strabismus treated with botulinum toxin in a general tertiary hospital over a 10-year period and analyze the outcome of treatment.

**Subject, material and methods**

We performed a retrospective study of patients aged  $\geq 18$  years and diagnosed with acquired restrictive strabismus treated with botulinum toxin (Botox®, Allergan Inc., Irvine, CA, USA) between January 2002 and December 2012 in the Ocular Motility Section of our hospital. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón.

The inclusion criterion was acquired restrictive strabismus. For the purposes of the present study, restrictive strabismus was defined as any incomitant deviation secondary to Graves ophthalmopathy, high myopia, orbital conditions, and post-surgical complications (secondary to retinal detachment surgery, cataract surgery, and any other ocular surgery), with a positive forced duction test result and botulinum toxin as the initial treatment. Subsequent injections were not applied if an increasing deviation or patient objection were observed.

The exclusion criteria were congenital restrictive strabismus or fibrosis (e.g., Duane syndrome), infantile strabismus,

previous surgery of extraocular muscles, and follow-up of fewer than 6 months.

The data collected from the patient's medical records were age, sex, type of deviation (vertical, horizontal, or mixed), etiology, diplopia, head turn, extent of deviation in primary position before treatment, time (months) from the onset of symptoms to the first injection, number of injections, total dose, and complications during administration. The other data recorded after administration of botulinum toxin were post-operative deviation in primary position, head turn, diplopia, need for prism glasses, surgical treatment, and follow-up from the first injection to the end of the study.

Vertical and horizontal deviations in primary position were measured using the simultaneous prism and cover test at far and near distance; the greatest deviation was used for the statistical data analysis. The forced duction test was performed in the operating room immediately before botulinum toxin was administered. The drug was always administered under topical anesthesia (lidocaine 2%) with cardiac and electromyographic monitoring in the operating room and an anesthesiologist present.

A successful outcome was considered to be a vertical deviation  $\leq 5$  PD, horizontal deviation  $\leq 10$  PD, absence of

diplopia and head turn at the end of follow-up, with no need for additional treatment (prism glasses or surgery). A descriptive analysis was performed using IBM SPSS Statistics for Windows Version 22.0 (IBM Corp, Armonk, New York, USA).

## Results

A total of 27 cases were included in the study. The mean age of the sample was  $61.9 \pm 15.6$  years (range, 29–83 years), and 52% were women (14/27). As for diagnosis, 51.9% had vertical restrictive deviation, 37% mixed vertical and horizontal deviation, and 11.1% horizontal deviation. Strabismus was secondary to cataract surgery with sub-Tenon anesthesia in 6 cases (22%), high myopia in 6 cases (22%), orbital fracture in 5 cases (18.5%), retinal detachment surgery in 5 cases (18.5%), Graves ophthalmopathy in 4 cases (15%), and conjunctival surgery in 1 case (4%).

Table 1 shows pre-treatment and post-treatment patient data. All patients had diplopia, and 33.3% had head turn at diagnosis. The initial deviation was  $14 \text{ PD} \pm 9.9$  (range, 2–40 PD). The mean number of injections per patient was  $1.6 \pm 0.7$  (range, 1–3), and the mean dose was  $9.5 \pm 4.8 \text{ IU}$

**Table 1** Pre-treatment and post-treatment data.

Case	Type	Pathology	D/T	Time until first injection (months)	No. of injections/dose (IU)	Pre-treatment deviation in PP	Final deviation in PP	Final D/T	S/P	Result
1	H	HM	Y/Y	6	2/15.0	10	30	N/Y	Y/N	Bad
2	V	HM	Y/Y	1	2/17.5	5	0	N/N	N/N	Good
3	M	HM	Y/N	5	1/2.5	18	2	N/N	N/Y	Good
4	H	HM	Y/Y	1	1/2.5	14	0	N/N	N/N	Good
5	V	HM	Y/N	2	2/10	25	16	Y/N	Y/N	Bad
6	V	HM	Y/N	1	3/15	12	4	N/N	N/N	Good
7	V	GO	Y/Y	2	2/10	18	33	Y/Y	Y/N	Bad
8	V	GO	Y/Y	1	1/10	5	8	Y/N	N/N	Bad
9	H	GO	Y/N	1	2/10	12	8	Y/N	Y/N	Bad
10	M	GO	Y/N	1	1/5	3	12	Y/N	Y/N	Bad
11	M	Post RD surg	Y/N	2	1/5	8	4	N/N	N/Y	Good
12	M	Post RD surg	Y/N	2	1/5	12	30	Y/N	Y/N	Bad
13	V	Post RD surg	Y/N	1	1/10	25	40	Y/N	Y/N	Bad
14	M	Post RD surg	Y/N	4	1/7.5	40	6	Y/N	N/N	Bad
15	V	Post RD surg	Y/N	1	3/16	5	0	N/N	N/N	Good
16	M	Fx	Y/Y	1.5	2/10	10	16	Y/Y	Y/N	Bad
17	M	Fx	Y/Y	1	1/10	5	2	N/N	N/N	Good
18	V	Fx	Y/N	3	1/10	10	0	N/N	N/N	Good
19	M	Fx	Y/N	2	1/5	6	1	N/N	N/N	Good
20	V	Fx	Y/Y	1	3/22.5	30	35	Y/Y	Y/N	Bad
21	V	Post cat surg	Y/N	1	1/3	8	30	Y/Y	Y/N	Bad
22	V	Post cat surg	Y/N	2	1/4	30	25	Y/N	Y/N	Bad
23	M	Post cat surg	Y/N	1	3/15	2	8	N/N	N/Y	Good
24	M	Post cat surg	Y/Y	2	1/10	30	18	Y/N	Y/N	Bad
25	V	Post cat surg	Y/N	1	1/7.5	8	14	Y/N	N/Y	Bad
26	V	Post cat surg	Y/N	2	2/10	16	18	Y/N	Y/N	Bad
27	V	Post conj surg	Y/N	3	2/10	12	16	Y/N	Y/N	Bad

Type: strabismus type; V: vertical; H: horizontal; M: mixed; HM: high myopia; GO: Graves ophthalmopathy; Fr: orbital fracture; post RD surg: post-retinal detachment surgery; post cat surg: post-cataract surgery with sub-Tenon anesthesia; post conj surg: post-conjunctival surgery; D: diplopia; T: torticollis; Y: yes; N: no; PP: primary position; S: surgery after treatment with botulinum toxin; P: need for prism glasses after treatment with botulinum toxin; IU: international units.

**Table 2** Successful outcome according to type of restrictive strabismus.

Type of restrictive strabismus	Total (no. of cases)	Successful outcome (no. of cases)	Percentage
High myopia	6	4	66.66
Orbital fractures	5	3	60
Retinal detachment surgery	5	2	40
Graves ophthalmopathy	4	0	0
Cataract surgery	6	1	16.66
Conjunctival surgery	1	0	0

(range, 2.5–22.5 IU). One injection was applied in 55.5% of patients (15/27), 2 injections in 29.6% (8/27), and 3 in 14.8% (4/27). The mean time from onset of the symptoms until the first injection was  $1.9 \pm 1.3$  months (range, 1–6 months). The final deviation in primary position was  $13.9 \pm 12.4$  PD (range, 0–40 PD). At the end of follow-up, 59% of patients had diplopia, 18% had head-turn, 52% needed surgery after botulinum toxin, and 14% needed treatment with prisms. Outcome was successful in 10 patients (37%): 4 high myopia (40%), 3 orbital fractures (30%), 2 post-retinal detachment surgery (20%), and 1 secondary to cataract surgery with sub-Tenon anesthesia (10%). Table 2 shows successful outcome according to the type of restrictive strabismus. We have not recorded any complications during administration of botulinum toxin. The mean follow-up was 3 years  $\pm$  1.8.

The small sample size in each etiologic group did not enable us to draw conclusions about the influence of the etiology on the outcome of treatment.

## Discussion

Acquired restrictive strabismus can be secondary to a series of conditions including high myopia, Graves ophthalmopathy, orbital conditions (fracture, myositis, metastasis), and procedures to correct retinal detachment, glaucoma, cataract, and conjunctival disorders. The treatment options recommended to eliminate deviation were surgery on the extra-ocular muscles and botulinum toxin.<sup>1–3,6,11</sup> However, botulinum toxin is not as effective in restrictive strabismus as in comitant strabismus and oculomotor nerve palsy. More injections and doses are necessary.<sup>3</sup> In our study, a favorable outcome was obtained in 37% of cases, which is lower than in other types of strabismus such as acquired and congenital esotropia (60–80%), intermittent exotropia (69%), and oculo-motor nerve palsy (70%).<sup>12–15</sup>

The effect of botulinum toxin depends on etiology. In our sample, a favorable result was not achieved in any of cases of thyroid strabismus (2 vertical, 1 horizontal, and 1 combined horizontal and vertical) at the end of follow-up. In every case, botulinum toxin was administered very early (1 and 2 months from the onset of symptoms). In 3 cases, 10 IU were administered, and in 1 a total of 5 IU. Lyons et al.<sup>5</sup> obtained good results in 15.78% of cases with botulinum toxin, and the deviation decreased by 75%, although 68.42% of patients needed strabismus surgery after the injections. The benefit obtained with botulinum toxin could be associated with the relaxation of the inflammatory spasm that is

characteristic of the acute phase of the illness. Botulinum toxin is less effective in muscle fibrosis and contracture.<sup>5</sup> Wu et al.<sup>3</sup> reported resolution in 15 of 33 cases (45.45%) and decreased deviation in 12 (36.36%). Administration must be early, with a mean dose of 8 IU and subsequent injections. Another benefit of botulinum toxin is the decrease in intra-ocular pressure in primary position and in supraversion 2–4 months after injection in the inferior rectus.<sup>16,17</sup>

At the end of follow-up, outcome was successful in 4 of 6 cases (66.66%) of strabismus associated with high myopia. Treatment was applied early in each case (within <6 months after the onset of symptoms), and the total dose was 2.5–17.5 IU. Few publications in the literature analyze treatment with botulinum toxin for acquired restrictive strabismus secondary to high myopia. The best results are achieved in young patients with poor binocular vision and severe amblyopia because of the neurosensory adaptation following therapy with botulinum toxin. Botulinum toxin has also proven effective in post-surgical over-correction and under-correction.<sup>11,18–20</sup>

Botulinum toxin is not effective for restrictive strabismus secondary to ocular surgery for several reasons, including extensive fibrosis and displacement of the superior and inferior oblique muscles after surgery to correct glaucoma and retinal disorders. The frequency of successful outcome varies widely (15–85%).<sup>8,21</sup> The sub-Tenon anesthesia used in cataract surgery is responsible for diplopia and restrictive strabismus secondary to muscle contracture, fibrosis, and palsy. Botulinum toxin is effective in only 25% of cases of muscle palsy, before development of muscular fibrosis, which is frequent and has an early onset in older patients.<sup>7</sup> In our study, outcome was successful in 40% (2/5) of cases secondary to retinal surgery, in which botulinum toxin was injected early (1–4 months after onset of symptoms). Six cases were secondary to sub-Tenon anesthesia for cataract surgery, although outcome was successful after early injection (1 and 2 months from the onset of symptoms) in only 1 case (16.66%).

Restrictive strabismus can be secondary to orbital conditions such as fractures, myositis, neoplasm, and metastasis.<sup>4</sup> In our sample, outcome was successful in 3 of 5 cases (60%) of orbital fractures after early treatment with botulinum toxin (within <3 months), with total doses of 5–22.5 IU and 1–3 injections. Lee et al.<sup>6</sup> reported good results in 69% of patients with orbital conditions, 67% of patients with myositis, and 33% of patients with fractures. The benefit was independent of the angle of deviation.

Our study is limited by its retrospective nature and the small number of patients in each group. In addition, it was

not possible to analyze the effect of etiology on outcome. Nevertheless, the follow-up period was long enough to draw conclusions about the stability of botulinum toxin for treatment of acquired restrictive strabismus.

In conclusion, half of the patients in this sample had vertical deviation. The most frequent etiology was sub-Tenon anesthesia for cataract surgery and high myopia. Botulinum toxin was effective in only one-third of the patients at the end of follow-up, and outcome was similar for high myopia, orbital fractures and retinal detachment surgery. The results were worse in cataract surgery, and botulinum toxin was not effective in Graves ophthalmopathy and conjunctival surgery. Half of the patients needed extra-ocular muscle surgery after treatment with botulinum toxin. Botulinum toxin can be considered a complementary or alternative approach to surgery in some complex cases of acquired restrictive strabismus.

### Conflicts of interest

The authors have no conflicts of interest to declare.

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