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Original scientific paper

Treatment of Ocular Motility Disturbances in Graves' Disease with Botulinum Toxin A

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A B S T R A C T

The aim of this study was to evaluate the efficacy of botulinum toxin-A injections on motility disturbance in patients with dysthyroid eye disease. In 36 patients (52 orbits) with active phase of Grave's ophthalmopathy with motility disturbance, botulinum toxin-A injections were applied. Ocular motility was measured before and after treatment in four main directions (elevation, depression, abduction and adduction) with Förster perimeter. In all patients 20 units of botulinum toxin-A in one single injection was applied in the projection of the inferior rectus muscle. Statistically, the degree of upgaze increased notably in all three groups, but mostly in the first group where it amounted up to 5.8–6.0 (z=10.0; p=0.68). We could not prove notable increase of the motility grade in the adduction in none of the groups of the tested patients. Due to the fact that eyeball motility can be objectively measured, effect of the applied therapy can be clearly evaluated.

Key words: *Graves' disease, dysthyroid orbitopathy, botulinum toxin-A, motility disturbance*

Introduction

Graves' disease is an autoimmune disorder, very often coexisting with dysfunction of the thyroid gland. Three main features of the disease are orbitopathy, dermopathy and acropacy. Orbitopathy is manifested as swelling of the soft tissue, dysfunction of the extraocular muscles, proptosis, eyelid retraction, optic neuropathy and secondary keratopathy.[1] Orbitopathy can be in active and inactive phase.[2,3] The exudative phase represents a turbulent immunity reaction of the cellular and humoral type in the fibroblasts of orbital tissue.[4–8] The dominant changes of the orbital structures are on the extraocular muscles in terms of thickening, but without structural changes of the myofibrils.[4,8,9] The diminished elasticity of the extraocular muscles in the active phase of the disease is primarily caused by active contraction of the muscles and not by fibrosis.[10]

The aim of the treatment is to shorten or to stop the active phase of the disease, to reduce the retrobulbar pressure, to free the motility and postpone or prevent the muscle fibrosis. The culmination of the disease is opticoneuropathy with secondary glaucoma and the consecutive permanent loss of sight. The corticosteroids applied in the early phase either as a systemic therapy or locally in the form of parabulbar injections, does not show a satisfactory effect on the motility (only in 30% of patients).[11,12] On the other hand, 60% of patients with Grave's orbitopathy treated with protracted high dosages of corticosteroids[13] showed a satisfactory effect on the dysfunction of the extraocular muscles. The effect of radiotherapy on the motility is also not satisfactory.[14]

Botulinum toxin-A has been used in ophthalmology since 1981 in the treatment of squint, focal dystonias as blepharospasmus, retraction, spastic entropium and for headaches as result of fusion effort.[15–17] In 1998, H. J. Simonsz published paper describing recovery of the vision in patients treated with botulinum toxin-A injections. So far the botulinum toxin A has been investigated in the therapy of dysthyroid squint. If injected in the lower rectus muscle within one year after the appearance of the diplopia it improves the eye motility, which means that the active contraction is present even after a relatively long-time persistent diplopia.[18]

Patients and Methods

The testing was carried out prospectively in the period from 1999 until 2001 on 36 patients. There were 29

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women and 7 men. The age of the women ranged from 36 to 69 years (mean age 46.9±7.5 years), and the age of men ranged from 46–66 years (mean age 56.9±7.6 years). The women were statistically notably younger (t=23.14; p=0.003). Out of 36 patients 27 were smokers and 9 non-smokers. All the patients were either euthyroid or with the stable hormonal status of the thyroid gland under the medication for at least two months. Before the therapy one patient was in hypothyreosis, 3 were euthyreotid and 32 in hyperthyroid. Considering the time of initial complaints and the onset of the thyroid gland disease, 13 eyes simultaneously developed symptoms of the thyroid and eye disease. In 29 eyes the eye symptoms appeared after the onset of the thyroid gland disease in median of 4 months.

Because of the statistical elaboration in our investigation as the testing unit we used the eye and not the patient. The number of eyes included in the analysis was 52. 23 were left and 29 right eyes.

Clinical manifestation defined the stage of dysthyroid orbitopathy, directed by several International thyroidal associations supplemented after the recommendations of CA Gorman.[19] The activity of the disease was determined using the clinical activity score concept (CAS). Its basis is 4 of 5 signs of the inflammation: pain, redness, swelling and disorder of the function. The disease is considered as dynamic if the CAS score is grater than 4.[21] The degree of the eyeball motility is measured due to recommendations of Mourits and collaborators.[21] We used the modified Foerster perimeter. The patient's head was fixed on a holder which is movable so the tested eye can be brought to wanted height and position. The other eye was closed. The bow of the perimeter calibre in degrees and in the centre of the bow we have placed a small lamp which we could move freely along the bow of the perimeter. We watched the reflex of the lamp light on the surface of the cornea. When the patient is unable to follow the light, the reflex would disappear and the value of the maximum excursion of the eye in the tested direction is noted. We measured four main directions of gaze. Elevation and depression with the bow of the perimeter vertically placed and adduction and abduction with the bow placed horizontally. We drew the results of the measuring in the prepared forms, for each eye separately.

Examination of all patients included in the study was performed before and after the treatment. Examination included inspection of the eyelids and cornea, ocular motility measurement, visual acuity, Hertel exophthalmometry, ophthalmoscopy and applanation tonometry. Ocular motility was examined before and after treatment in four main directions (elevation, depression, abduction and adduction) with Förster perimeter. Side effects in terms of the worsening of the diplopia (although we are aware that the positive influence of botulinum toxin A on severely disturbed motility can produce subjective perception of »worsening«) and the pain were noted. Botulinum toxin A (Botox-Allergan) is a vial of 100 units of the medication in the form of crystal powder. The powder is dissolved with 1.0 ml 0,9 % solution of natrium cloride so that 0.1 ml of the solution consist 10 IU of botulinum toxin A. 0.2 ml (20 IU) were applied with the insulin syringe which contains 1.0 ml of the solution.

In prospective study, 36 patients were assigned randomly to 1 of 3 different groups dependent of therapy applied before botulinum toxin A. The group 1 comprises 20 eyes who were treated with local protective therapy. Group 2 comprises 16 eyes treated with oral corticosteroids before the application of botulinum toxin A. In the third group there were 16 eyes treated with the puls corticosteroid therapy. (12.5 mg/kg Methylprednisolon in 250 ml 0.9% of the Natrium Cloride in the infusion during 60 min). All patients were given 20 IU of botulinum toxin A in projection of inferior rectus muscle. Follow up measuring the eye motility on Foerster perimeter was 15 days after the application, 30 days, 12 and 24 months.

The groups didn't significantly differ according to the age, the age range of the first group being 45.5±9.22 years (the span of 36–68 years) (X^2=2.9; p=0.23). The inclusive criteria for any group was the activity of the disease and the presence of the diplopia as a consequence of the disturbed eye motility. Two patients were excluded because of incomplete follow up.

The statistic analysis was performed using the statistical package SPSS 9.0. Following tests were used: t-test for independent samples, X^2 test, Mann-Whitney test and Kruskal Wallis analysis of the variance.

Results

The motility range has significantly increased in upgaze (elevation) in all three groups after botulinum toxin A was applied. In the first group it increased in 12 eyes (75%). The observed groups differed according to the range of upgaze before and after the applied therapy in terms of greater motility in the first group. The second and the third group did not differ significantly in the range of motility neither before nor after the therapy (z=1.0; p=0.31) (z=0.42; p=0.6858) so it can be concluded that the effect of both previously given therapies was the same. The motility change in the second group amount to 4.6±3.9 (0.13) and in the third group 2.6±2.70 (0–10)

The change of the motility range in the first group was statistically significantly greater than in the second and the third group and it amounted to 5.8±6.0–25 (X^2=10.0; p=0.005). Statistically significant was the increase of downgaze (depression) in all three groups. In the first group it increased in 18 (90%) eyes. Statistically the groups differ significantly in the degree of downgaze before and after the threatment but there were no significant differences in the change of downgaze degree in the examined groups. In the first group the change of the downgaze degree was 5.3±4.9 (–5 to 13), in the second group 2.4±3.3 (–5 to 9) and in the third group 3.1±3.6 (–1 to 12) (X^2=3.8; p=0.15).

TABLE 1
THE SURVEY OF THE AVERAGE VALUE, STANDARD DEVIATION AND THE SPAM OF THE UPWARD (ELEVATION) MOTILITY GRADE BEFORE AND AFTER THE THERAPY

Group of patients Modality of treatment	N	The motility grade		z	p
		Before	After		
No other treatment before botulinum toxin A	20	16.4±9.3 (4–38)	22.1±8.7 (14–38)	3.6	0.000
Corticosteroids treatment before botulinum toxin A	16	8.7±5.4 (5–25)	13.3±4.8 (6–25)	3.4	0.001
Simultanously treated with corticosteroids and botulinum toxin A	16	11.5±7.8 (1–25)	14.1±8.2 (1–25)	3.1	0.002
		χ^2=10.5; p=0.007	χ^2=11.6; p=0.003		

TABLE 2
THE SURVEY OF THE AVERAGE VALUE OF THE STANDARD DEVIATION AND AND DOWNWARDS (DEPRESSION) MOTILITY GRADE BEFORE AND AFTER THE TREATMENT WITH BOTULINUM TOXIN A

Group of patients	N	The motility grade		z	p
		Before	After		
No other treatment before botulinum toxin A	20	27.5±7.4 (10–40)	32.8±7.7 (20–52)	3.5	0.001
Corticosteroids treatment before botulinum A	16	25.6±5.6 (15–35)	28.0±4.3 (20–35)	2.3	0.022
Simultanously treatment with corticosteroids and botulinum toxin A	16	19.5±9.7 (3–30)	22.6±9.4 (3–32)	2.8	0.005
		χ^2=6.9; p=0.03	χ^2=16; p=0.000		

TABLE 3
THE SURVEY OF THE AVERAGE VALUE OF THE STANDARD DEVIATION AND THE SPAM OF ADDUCTION BEFORE AND AFTER THE TREATMENT WITH BOTULINUM TOXIN A

Modality of treatment	No	The motility grade		z	p
		Before	After		
No other treatment before botulinum toxin A	20	31.1±6.2 (17–40)	33.1±7.6 (20–45)	1.5	0.13
Corticosteroid therapy before botulinum toxin A treatment	16	25.9±10.7 (5–45)	27.4±7.5 (15–40)	1.13	0.26
Treated simultaneously with corticosteroids and botulinum toxin A	16	25.4±11.7 (4–45)	26.0±12.1 (4–45)	1.25	0.21
		χ^2=3.9; p=0.14	χ^2=4.7; p=0.09		

We have not proved statistically significant increase in adduction degree in neither of the tested groups.

In the first group the increase occurred in 18 and in second group in 16 eyes, whereas in the third group it

TABLE 4
THE SURVEY OF THE AVERAGE VALUE OF THE STANDARD DEVIATION AND THE SPAM OF THE ABDUCTION BEFORE AND AFTER THE TREATMENT WITH BOTULINUM TOXIN A

The modality of the treatment	N	The motility grade		z	p
		Before	After		
No other treatment before botulinum toxin A	20	29.2±7.5 (10–43)	33.6±6.8 (25–45)	3.5	0.000
Corticosteroids treatment before botulinum toxin A	16	17.8±7.3 (6–35)	27.3±7.7 (12–40)	3.5	0.000
Treated simultaneously with corticosteroids and botulium toxin A	16	26.6±12.3 (7–40)	28.8±10.8 (7–40)	2.02	0.044
		χ^2=12.6; p=0.002	χ^2=4.3; p=0.11		

occurred in 10 eyes. Statistically, groups differed significantly in the abduction degree in all three groups, abduction being the least in the second group. After the therapy there were no significant differences in the abduction degree among the groups. The greatest change developed in the second group. The change of the abduction degree in the second group was 2.3±6.2 (–10 to 20) (X^2=14.3; p=0.001).

TABLE 5
THE SURVEY OF THE FREQUENCY OF THE EYE MOVEMENTS RANGED BETWEEN 10 DEGREES BEFORE AND AFTER THE TREATMENT WITH BOTULINUM TOXIN A

		Number of the eyes	
		Before	After
Elevation (degrees)	<10	23	9
	11–20	20	28
	21–30	7	11
	31–40	2	4
Depression (degrees)	<10	3	2
	11–20	12	3
	21–30	16	15
	31–40	19	30
	41–50	2	2
Abduction (degrees)	<10	3	2
	11–20	6	4
	21–30	15	21
	31–40	24	17
	41–50	4	8
Adduction (degrees)	<10	4	2
	11–20	12	2
	21–30	16	17
	31–40	15	21
	41–50	5	10

Motility was measured on Forster perimeter in degrees as it was explained before. Patients were grouped in three groups with 10 degrees range between. The best effect of botulinum toxin A was depicted in the elevation: 8 eyes in group with movements between 11–20 degrees, 4 in group between 21–30 degrees and 2 eyes in group with movements between 31–40 degrees. There was no improvement in adduction. In 12 eyes the abduction was less then 21 degrees before the therapy, but after the therapy only 2 eyes remained in this group and 19 moved to the group with grater motility.

In 2 patients from the third group diplopia worsened and occlusion to one eye was applied for certain time. Complications such as ptosis of the upper eyelid, epiphora or pain didn't occur.

Discussion

The dysthyroid orbitopathy is an autoimmune disorder which is manifested r with an autoimmune disease of the thyroid gland. Sometimes it goes together with dysfunction of the thyroid gland as hyper function (in most of the cases) or hypo function of the thyroid gland. Euthyroid function of the thyroid gland doesn't exclude autoimmune disorder with dysthyroid orbitopathy. Orbitopathy is present in almost all patients with hyperthyreosis, but only in some patients it appears in its full clinical presentation.[22,23]

Dysthyroid orbitopathy is the most frequent cause of the uni or bilateral proptosis in adults. It is also the most frequent pathology of the orbit in adult persons.[21] The disease appears most often in women whereas in men it appears later and some times in more serious form.[22,24] This investigations approved the same distribution among the sex and age. The majority of patients were active smokers which correspond to the data from the literature. The functional status of the thyroid gland did not show the exemptions from the noted in literature. The great majority of patients were hyperthyreotic. In most of the cases orbitopathy developed after the

resolution of the thyroid gland disease.[22–25] CAS classification account four signs of inflammation to present the activity of the disease[20,26]: pain, redness, swelling and function disorder. Redness of caruncula is especially characteristic sign of active phase of the disease. The swelling of the orbital soft tissue presents with periorbital oedema, chemosis and proptosis. Disturbance of the eye motility is present in 60 % of patients in the active phase of the dysthyroid orbitopathy. It is caused by the active muscle contraction which was determinede by electromyography and some other clinical investigations as changes in T time on MRI.[8,10,18,27]

Inferior rectus muscle is affected in most of the cases, often together with medial rectus muscle or superior muscles complex (rectus superior and levator muscle) Lateral rectus muscle is rarely affected and it is a case in malignant active phase of the disease (Grave's disease), when all extraocular muscles are enormously enlarged. The speculation is that hypoxia of medial portion of the orbital contents is essentially present due to anatomical relationship of the orbital contents and circulation in the orbit. So any chronic or acute stress of the orbital circulation can be the trigger to develop dysthyroid orbitopathy. Corticosteroids are the therapy of choice in active phase of the disease and depending on the grade of the disease it can be applied locally as eyedrops or as parabulbar injections in projection of affected muscle. In moderately severe, or severe, vision threatening forms of the disease, corticosteroids are given systemically as pulse therapy or in lower doses through prolonged period of time. Radiotherapy is also considered in lower grades of CAS activity as singular therapy or in combination with corticosteroids. Such kind of treatment did not give satisfactory results in the improvement of the eye motility (30–60 %) and it was subjected to different contraindications and a greater risk of the complications and side effects.[12–14]

The effect of botulinum toxin A causes relaxation of the transversally striped and smooth muscles. Such pseudoparesis last from 60 to 90 days.[28,29] Hyperfunction of the corrugator supecilii muscle results partly due to the effort of fusion which occurred owing to the latent diplopia in patient with dysthyroid orbitopathy. For the same reason botulinum toxin A was used in patients with pronounced retraction of the upper eyelids. In most of the cases retraction of the upper eyelids is result of the motility disturbance of inferior rectus muscles. The therapy with botulinum toxin A in such cases has to be in projection of the inferior rectus muscles as well as in projection of the upper retractors muscles.[16,17]

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BOTULINUM TOXIN A U LIJEČENJU POREMEĆAJA BULBOMOTORIKE KOD PACIJENATA SA GRAVESOVOM BOLEŠĆU

S A Ž E T A K

Cilj rada je procjena utjecaja botulinum toxina A na bulbomotoriku kod pacijenata sa distiroidnom orbitopatijom. U istraživanje su uključena 32 pacijenta (52 orbite) s aktivnom fazom bolesti i poremećenom bulbomotorikom apliciran je botulinum toxin A u obliku injekcija. Pokretljivost bulbusa u četiri osnovna smjera mjerena je prije i poslije tretmana na Forster perimetru. Kod svih pacijenata aplicirano je jednokratno 20 IJ botulinum toxina A parabulbarno u projekciji m. rectus inferiora. Statističkom obradom podataka stupanj elevacije značajno se povisio u sve tri grupe, s najvišim porastom u prvoj grupi gdje je iznosio 5,8-6,0 (z=10,0; p=0,68). Statistički nije dokazan relevantan porast stupnja adukcije ni u jednoj grupi.Obzirom na činjenicu da se motilitet bulbusa može objektivno mjeriti, utjecaj botulinum toxina A na promjenu bulbomotorike također se objektivno može pratiti.