ORIGINAL ARTICLE

The Application of Dysport® - the Possibilities of the Side Effect on the Eyelids Position (a Clinical – Histological study)

[1]Krásný J., [2]Šach J. J.

[1]Ophthalmic Clinic of Faculty Hospital, Prague, Head of the Clinic: P. Kuchynka
[2]Department of Pathology, 3. Medical Faculty and Faculty Hospital, Prague, Head of the Department: V. Mandys

SUMMARY

The Application of Dysport® – the Possibilities of the Side Effect on the Eyelids Position (a Clinical – Histological study)

Aim: To inform about the possibility of negative influence of repeated application of the botulotoxine A derivate on the eye lid position with the changes of their tissue structure. At the same moment, the authors report on literature analysis of positive and negative influence of this neuro toxine from the medical point of view.
Materials and methods: At the Department of Ophthalmology in the Faculty Hospital Královské Vinohrady, Prague, Czech Republic, E.U., there were surgically treated three patients after repeated applications of botulotoxine A derivates. The first case was bilateral ptosis of upper eyelids; the other two were indicated
because of entropium with trichiasis of lower eyelids. In the medical history, there was recorded ten years lasting above-mentioned drug treatment for blepharospasm diagnosis in a 65 years old man introducing bilateral symmetrical ptosis. Because of the following frontal muscle involvement, and partial decreasing levator palpebrae muscles function, the positioning of the upper eyelids was treated by the aponeurosis plasty with good functional result. In two female patients, aged 72 and 90 years, the indication for successful surgical treatment was chronic entropium of lower eyelids; initially ineffectively treated by means of repeated intradermal injections of botulotoxin A derivates.
Results: Histological examinations of the excided skin and subcutis samples taken during ectropium plasties showed unfavorable and irreversible changes including especially scarring of the eyelid and atrophy of the striated muscles. Conclusion: The indication of botulotoxine A derivates application should be carefully weighted and the proper indication should be chosen. From the ophthalmologic point of view, blefarospasmus only is the appropriate diagnosis, and the relative indication is the temporary induced ptosis of the upper eyelid closing the interpalpebral fissure to prevent corneal changes in lagophthalmos of various etiologies as an alternative to the tarsoraphy. Always we have to consider the frequency of applications, because repeatedly used derivate of this neurotoxine causes irreversible changes in cutaneous and subcutaneous tissue.

Key words: Botulotoxine A, entropium, histology, ptosis, treatment side effect

Čes. a slov. Oftal., 68, 2012, No. 5, p. 216–220

First author:
MUDr. Jan Krásný
Ophthalmic Clinic of Faculty Hospital, Prague
Šrobárova 50
100 34 Prague 10,CZ
E mail: jan.krasny@fnkv.cz

INTRODUCTION

Botulotoxin is a natural bacterial toxin produced by the anaerobic spore-forming rod-shaped bacterium Clostridium botulinum, which causes serious illnesses in humans characterised by means of a blockade of cholinergic neuromuscular transmission. The actual effect resides in a blockade of the release of acetylcholine in the presynaptic membrane of the neuromuscular junction. The process takes place in three phases: the precondition is linkage to the receptor, internalisation i.e. transition across the presynaptic membrane by active transport, and the result is actual intracellular blockade of acetylcholine. This principle is used in the treatment of local muscular spasms. As a result botulotoxin is evidently the most toxic substance used as a pharmaceutical medicament [25]. Botulotoxin was first defined and used by the German doctor Kerner in 1820.
In addition to neurology, the principle of blockade of cholinergic neuromuscular transmission has been applied also in ophthalmology, which was the pioneer of its use. Professional ophthalmological publications constitute 3% of medical quotations on the theme of the problem of botulotoxin over the last 15 years. At approximately the same time (1980s), botulotoxin began to be used in the therapy of blepharospasm and strabismus. In the last twenty years it has also been used as an alternative to temporary adjustment of the position of the upper eyelid, where lagophthalmos endangers the cornea due to drying.
The use of a derivate of botulotoxin A is at present being widely applied and enjoying a boom in consumer societies of modern industrial states primarily in the field of cosmetic medicine. The response of the pharmaceutical industry in developing new products

also corresponds to this trend. After the original Onabotulinumtoxin A (Botox®) from the Allergan company in the late 1980s, in 1990 there appeared Abobotulinumtoxin A (Dysport®) from the Porton Down company, which later changed its name to Speywood. Further preparations are Incobotulinumtoxin A (Xeomin®) from the Metz Pharma company and licensed preparations on the basis of the above-named derivates of botulotoxin A: Azzulure® (Ipsen Ltd.), Reloxin® (Ipsen Pharama) or Meditoxin® (Medy-Tox). The basis of all of the above preparations is Clostridium botulinum type A toxin – haemaglutin complex, and as a result there is no significant difference between the effects of these injected pharmaceuticals [21, 23, 33, 37]. At present the most widely used derivate of this neurotoxin remains Botox®.

OUR GROUP OF PATIENTS

Pathological positions of eyelids were surgically treated at the Eye Clinic of the Faculty Hospital Královské Vinohrady between 2006 and 2008. Derivates of botulotoxin A were repeatedly applied to the affected areas or closest surrounding areas on the three adult patients sent for treatment. In all of these cases the derivate concerned was Abobutolinumtoxin A (Dysport®).

1. Ptosis

A 65 year old patient was treated for ten years by application of Dysport according to the classic scheme of four application points for the condition of anamnestically indicated bilateral blepharospasm persisting for 15 years, which was diagnosed and treated in a neurological centre outside of Prague. A total of 140 IU(= international units) was always applied to both eyelids in a single session, at least four times per year. In the last three years before the surgical procedure indicated by us, a ptosis of both upper eyelids began to be manifested in direct connection with the application of Dysport. Although the condition was transitional, it gradually intensified. As a consequence the result was unsatisfactory for the patient, since the resulting bilateral ptosis necessitated backward tilting of the head.

Upon the first outpatient examination at the Eye Clinic of FH(University Hospital)KV in January 2007 (three months after the last application of Dysport), only sudden closure of the palpebral aperture and inability to open the eyes upon instruction accompanied by tremor of the eyelids were determined, but not the classic image of blepharospasm with an image of spasms (fig. 1). After spontaneous pacification the width of the palpebral apertures was 2-3 mm (fig. 2), the margopupillary diameter on the right eye 0, on the left eye 1 mm. The function of the levators was restricted to 4-6 mm, palpation of the area of the frontal muscle in the lower half was stiff, without signs of ability of functional involvement in supporting the lifting of the upper eyelids. Bilateral pseudofakia was accompanied by identical visual acuity in both eyes 1.0 nat. With regard to the limited function of the levators of both eyes and the functional affliction of the m. frontalis, the condition was treated by plastic operation of aponeurosis using two Prolen 6-0 “X” stitches. Three months after the operation the palpebral apertures had a width of 7 mm and the margopupillary diameter 3 mm (fig. 3).

2. Entropium

A 90 year old patient was examined at the outpatient Eye Clinic of FHKV for persisting entropium of the lower left eyelid (fig. 4) in April 2007. Repeated injections of Dysport were administered anamnestically over the course of 3 years, only with a temporary effect, as stated by the patient. The patient was well aware of this condition, since the afflicted eye was dominant, visual acuity 0.25 with correction +10.0D comb. +1.5D ax120° for postoperative aphakia. In the right eye the vision was decreased to hand motion in front of the eye with regard to severe amblyopia accompanied by a divergence ex anopsia. Over the course of 3 applications from June 2003 to November 2005, 100 IU was always administered into the lower eyelid in five points.

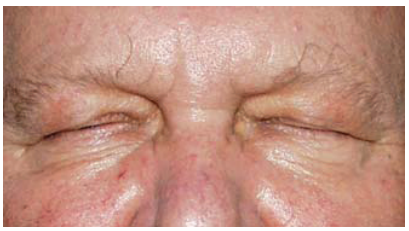

Fig. 1 Condition of position of eyelids at the time of attack – closure of palpebral aperture

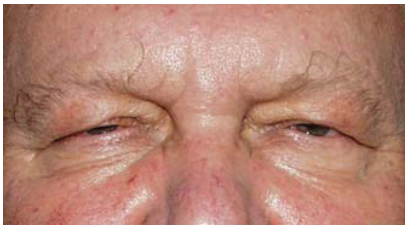

Fig. 2 Condition of position of eyelids at the time of relaxation – opening of palpebral aperture

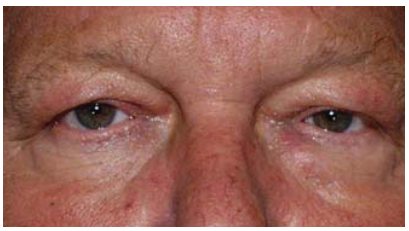

Fig. 3 Condition of position of eyelids after bilateral plastic operation of aponeurosis of upper eyelids

A 72 year old patient was examined in the same facility in February 2007 for bilateral entropium of the lower eyelids. Visual acuity bilaterally 0.66 with myopic astigmatism – 0.5D comb -1.5D ax100° in the right eye and 20° in the left eye. Anamnesis of administration of Dysport was longer, from October 2003 to June 2006, in total 120 to 160 IU was always applied to both lower eyelids of the patient in four points in eight sessions. The resulting effect was a persistence of entropium of the lower eyelids, since after injection of the neurotoxin the patient did not record a permanent effect or even a significant temporary improvement.

In both patients a classic picture of involution entropium was found upon our initial examination, characterised by a spontaneous rolling over of the lower eyelids against the eye upon instruction to close the eyes, which was not accompanied by spasms. Adjustment of the position of the eyelids was normalised by massage drawing of the skin downwards. Epiphora was only in connection with trichiasis. The condition was always treated by plastic operation of the lower eyelid with myrth cutting of the skin and subcutis down to the orbicularis muscle, which underwent partial resection in the surface layers. After electrocoagulation the surgical procedure was concluded only with skin traction stitches drawing in a downward direction. In the case of the first, older patient this was 6 months after the last application of Dysport and in the second, younger patient 9 and 11 months after the last injection. 3 months after the operations the position of the eyelids was normalised, the margo of both of the lower eyelids contoured the edge of the palpebral aperture well, and the condition was permanent (fig. 5).

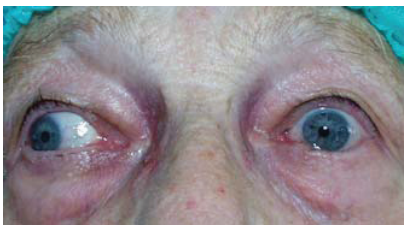

Fig. 4 Entropium and trichiasis of the lower left eyelid before the operation

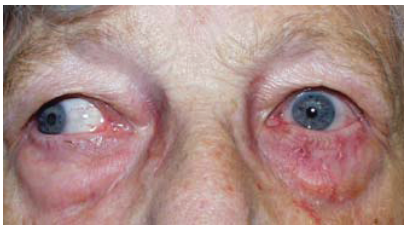

Fig. 5 Normalisation of the position of the left eyelid after the plastic operation

The results of histological examination from the resected parts of the skin and subcutis showed two types of pathological changes:
The first type of change was uneven scarring of the corium and adjacent subcutis, in places also with residual microscopic structures of non-specific granular tissue and microscopic residua of haematoma, evidently originating in connection with previous injection application (fig. 6). The second observed type of change was variably extensive atrophy of fascicles of the cross-striated muscle with attenuation of their individual fibres and repletion of the ligament in their interstitium (fig. 7) and with eventual chronic inflammatory infiltration (fig. 8).

DISCUSSION

The first scientif publications on the application of a derivate of botulotoxin A in ophthalmology, dating from 1980, is linked to the name of professor A.B.

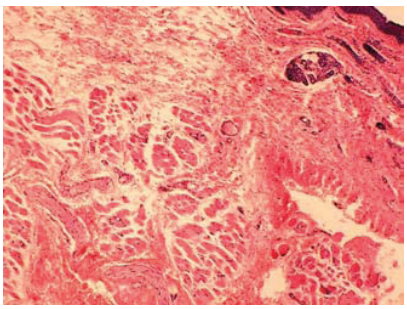

Fig. 6 Scarring of eyelid on surface with non-specific granular tissue and in the depth with residues of reabsorbing haematoma (colouring HE, enlargement 110x)

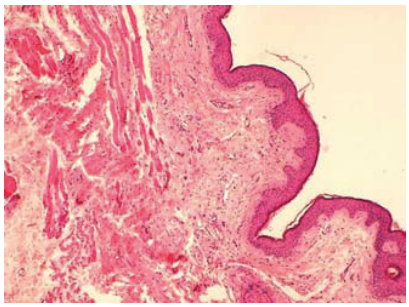

Fig. 7 Scarring and atrophy of muscle in eyelid and newly-formed ligament with small blood vessels of non-specific granular tissue (colouring HE, enlargement 100x)

Scott [30], who applied it in the treatment of strabismus as an alternative to a surgical procedure, whilst he first used it in 1973 [5]. This was later followed by publications of two working groups independent of one another [7, 31] upon the use of this neurotoxin in the treatment of blepharospasm in 1985. FDA approved the application of Botox® in 1989 in the indication of

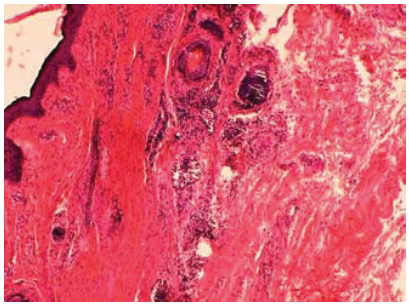

Fig. 8 Eyelid with significant manifestation with scarred, thickened ligament and chronic inflammation infiltration (colouring HE, enlargement 100x)

strabismus and blepharospasm, but not until 2002 for cervical dystonia.
At the turn of the millennium scientific articles appeared on the use of Botox® in the treatment of strabismus also in the region of former Czechoslovakia [8, 32]. Both publications in their time evaluated its use as very successful and classified it within the range of modern therapeutic tools. The success rate of administration of botulinum toxin from the perspective of two-year observation at present in infant esotropia above 60 pdpt is only 74%, i.e. with a residual deviation below 10 pdpt [15]. From this there ensues a certain caution with regard to indications of its applications, since it has a more variable result than classic surgical treatment [28]. The secondary side effects such as above all vertical deviation, as well as ptosis etc. [24] are decisively in favour of a negative standpoint, 24% in the case of Dysport and 55% in the case of Botox [28]. Although swelling and bleeding which also results from surgical procedures is included in these complications, negative motor changes are decisive for a negative evaluation.
An extensive study on 264 patients with blepharospasm concluded in 1988 demonstrated a fundamental therapeutic effect of a derivate of botulinum toxin A in the case of this disorder, unlike previously used avulsion of the facial nerve. A favourable effect of treatment was recorded in 57% of patients, of whom a significant improvement was recorded in 44%. In this study Abobotulinumtoxin A [10] was tested for the first time. This preparation was used in the first Czech applications [29] at the beginning of the 1990s. Transitional side effects include ptosis or diplopia in short-term observation [10]. All forms of injection products of botulintoxin A remain a fundamental medicament for blepharospasm at the present time [21, 34, 37].
In our first case, with regard to the previous ten-year anamnestic application of Dysport, the ptosis of the upper eyelids was now permanent. The impact of the above-stated neurotoxin is attested to by the loss of motor ability of the lower half of the frontal muscle, as well as symmetrical restriction of the function of both levators of the eyelids, caused by their regional and gravitational infiltration of neurotoxin from the forehead. The clinical picture of the position of the eyelids at the time of the ptosis operation rather approximated a picture of apraxia than classic blepharosmasm [19], but no verification of the findings in the preceding period was available any longer. The successful surgical procedure furthermore confirmed our consideration of lateral ptosis, since we did not perform frontotarsal suspension or resection of the levators, by which we avoided the afflicted structures.
In two more patients the reported diagnosis of spastic entropium was debatable with regard to age, since at this age involution form is considered, and in addition the clinical picture of our finding before plastic operation of the lower eyelids attested in favour of this involution form. The application of this neurotoxin in the treatment of entropium is not described by neuro-ophthal-

mologists. The performed previous intradermal applications of neurotoxins were shown to be ineffective, and in addition the entropic positions of the eyelids were conserved due to their developed trophic changes.

A further use of botulotoxin was applied in the treatment of retraction of the upper eyelid within the framework of Graves disease [4] in place of blepharorrhaphy as protection against affliction of the cornea by generating temporary ptosis [2, 16, 24]. Its application to the blockade of symptomatic epiphora [36] or in the treatment of difficult to influence filamentous keratitis [11] throws up a range of questions before it can be brought into regular practice.

Medical derivates of botulotoxin A have found application primarily in neurology, to which the neuro-ophthalmological problem of blepharospasm belongs. Its application to the eyelids has a beneficial influence on present oromandibular dystonia [10, 29]. The injection application of these pharmaceuticals is applied upon suppression of complaints in the case of facial spasms [3, 25] or independent cervical dystonias [21, 25] or in combinations thereof with migraines [35]. A further use of derivates of botulotoxin is described in the case of spasm of flexors of the ankle [10], or for tennis elbow [12].

Cosmetic medicine is very popular above all in the USA; out of a total sum of 11 billion dollars spent by clients in 2007, 3 billion alone was spent on the application of botulotoxin A, primarily Botox [17]. Wrinkles in the area of the forehead and periorbital region can be positively cosmetically influenced with the use of Botox, but this procedure is not approved by the FDA and considered off-label [13]. Ten years ago, upon an assessment of the results of more than one thousand patients following intradermal administration of botulinum toxin A in the facial area, no serious complications were described, but only the satisfaction of the clients with the resulting application [18]. After a certain period of time, isolated cosmetic surgeons began to become aware of the possibility of complications. After local applications there appears local pain and haematomas, headache, ptosis of the upper eyelids and eyebrows and a range of further changes [17, 23]. The described side effects in the orbital skin region following application of this neurotoxin also include change of pigmentation of the skin [26], rare herniation of the orbital fat [20] or pseudoaneurysm of the anterior branch of the superficial temporal artery [22]. Patients who have undergone a previous plastic operation in the given area with anamnesis of a neuromuscular disease or deep wrinkles are at a greater risk of complications [33]. A detailed study on the comparison of Botox with a placebo demonstrated a significant difference in the generation of ptosis and edema of the eyelids to the disadvantage of botulotoxin, but without overall manifestations on CNS [1]. Literary information states that even a one-off tenfold increase of the dosage of Botox as against the regular application given by mistake did not cause serious overall neurological manifestations [25, 29]. On the contrary, repeated applications may result in a general immunity response in risk individuals through the formation of antibodies against botulotoxin A [6].

Pathological-histological analyses of the side effects of derivates of botulotoxin A on skin tissue for necessary surgical procedures have not been evaluated by the specialists in the relevant disciplines. Of approx. 2000 quotations in PubMed up to 1997 there is only one independent histological study engaging with the animal model [8], which evaluates atrophic changes in the muscle, manifested in a change of the content of MyHC mRNA in muscle fibres. The application of Botox as such may lead to uncontrollable structural changes of the affected muscles. The authors are considering this clinical impact, the treatment of hypertrophic muscles using Botox may result in their functional imbalance. In our study there was irreversible atrophy of the cross-striated muscle of the eyelids in direct connection with the application of Dysport, and not due to the impact of involution changes, since the more marked changes were in the younger patient with more numerous applications of Dysport.

CONCLUSION

The authors wish to draw attention to histologically verified adverse changes in the structure of the skin and subcutis following repeated applications of a derivate of botulotoxin A, and to familiarise the professional public with this fact for its own consideration in personal use. It is not possible to assume that this shall in any way affect the frequency of administration in commercial cosmetic dermatology centres or private eye centres, despite the fact that it is considered an off-label application.

LITERATURE

1. Brin, M.F., Boodhoo, TI, et. al.: Safety and tolerability of onabotulinumtoxin A in the treatment of facial lines: a meta-analysis of individual patient data from global clinical registration studies in 1678 participants. J Am Acad Dermatol, 61; 2009: 961–970.
2. Choi, J.C., Lucarelli, M.J., Shore, J.V.V.: Use of botulinum toxin A in pacients at risk of wound complications following eyelid reconstruction. Ophthal Plast Reconstr Surg, 13; 1997: 259–264.
3. Clark, G.T.: The management of oromandibular motor disorders and facial spasm with injections of botulinum toxin. Phys Med Rehabil Clin N Am, 14; 2003: 727–748.
4. Costa, P.G., Saraiva, F.P., et al.: Comparative study of Botox injection treatment for upper eyelid retraction with 6-moth follow-up in patients with thyroid eye disease in the congestive or fibrotic stage. Eye, 223; 2009: 767–773.
5. Crouch, E.R.: Use of botulinum toxin in strabismus., Curr Opin Ophthalmol, 17; 2006: 435–440.
6. Dressler, D., Wohlfahrt, K., et al.: Antibody-induced failure of botulinum toxin a therapy in cosmetic indication. Dermatol Surg, 36; 2010, Suppl. 4: 2182–2187.
7. Eston, J.S., Russel, B.W.: Effect of treatment with botulinum toxin on neurogenic blepharospasm. Brit Med J, 290; 1985: 1857–1859.
8. Gedrange, T., Gredes, T., et al.: Histological changes and changes in the myosin mRNA content of the porcine masticatory muscles after masseter treatment botulinum toxin A. Clin Oral Investig, 2012, Springer, (v předstihu publikováno na PubMed).
9. Gerinec, A., Slyško, P., Fišerová, O.: Prinos botulotoxínu v liečbě strabizmu. Čes a Slov Oftal, 54; 1998: 174–178.
10. Grandas, F., Elston, J., et al.: Blepharospasm: a review of 264 patients. J Nerol Neurosurg Psychiat, 51; 1988: 767–772.

11. Gumus, K., Lee, S., et al.: Botulinum toxin injection for the management of refractory filamentary keratitis. Arch Ophthalmol, 130; 2012: 446–450.
12. Hayton, MJ., Dantini, A.J., et al.: Botulinum toxin injection in the treatment of tennis elbow. A double--blind, randomized, controlled, pilot study. J Bone Joint Surg Am, 87; 2005: 503–507.
13. Klein, A.V.V.: Botox for the eyes and eyebrows. Dermatol Slin, 22; 2004: 145–149.
14. Kowal, L., Wong, E., Yahalon, C.: Botulinum toxin in the treatment of strabismus. A review of its use and effects. Disdabil Rehabil, 23; 2007: 1823–1831.
15. Lueder, G.T., Galli, M., et al.: Longterm reset of botulinum toxin-augmended medial rectus recessions for largeangle infantile esotropia. Am J Ophthalmol, 153; 2012: 560–563.
16. Naik, M.N., Gangopadhyay, N., et al.: Anterior chemodenervation of levator palpebrae superioris with botulinum toxin type-A (Botox) to induce temporary ptosis for corneal protection. Eye, 22; 2008: 1132–1136.
17. Niautu, J. 3rd: Complications in Fillers and Botox. Oral. Maxillofac. Surg Clin North A, 21; 2009: 13–21.
18. Niautu, J. 3rd.: Botulin toxin A: a review of 1.085 oral and maxillofacial patient treatments. J Oral Maxillofac Surg, 61; 2003: 317–324.
19. Otradovec, J.: Klinická neurooftalmologie, Grada, Praha, 2003, s. 339.
20. Paloma, V., Samper, A.: A complication with the aesthetic use a Botox: Herniation of the orbital fat. Plast Reconstr Surg, 107; 2001: 1315.
21. Pagen, F.L., Harrison, A.: A guide to dosing in the treatment of cervical dystonia and blepharospasm with XeominR: new botulin neurotoxin A. Parkinsonism Relat. Disord., 18, 2012: 441–445.
22. Prado, A., Fuentes, P., et al.: Pseudoaneurysm of the frontal branch of the superfacial temporal artery: an unusual complication after the injection of Botox. Plast. Reconstr. Surg., 119, 2007: 2334–2335.
23. Prager, W., Huber-Vorländer, J., Taufig, A,Z.. et al.: Botulinum toxin type A treatment to the upper face: retrospective analysis of daily practice. Clin Cosmet Investig Dermatol, 5; 2012: 53–56.
24. Reddy, U.P., Woodward, J.A.: Abobotulinum toxin A (Dysport) and botulinum toxin type A (Botox) for purposeful induction of eyelid ptosis. Ophthal Plast Reconstr Surg, 26; 2010: 489–491.
25. Remeš, F., Roth, J., Růžička, E.: Léčebné použití Botulotoxinu v neurologii. Prakt Lék, 74; 1994: 174–177.
26. Roehm, P.C., Perry, J.D. et al.: Prevalence of periocular depigmentation after repeated botulin toxin A injections in African American patients. J Neroophthalmol, 19; 1999: 7–9.
27. Rousseaux, M., Buisset, N., et al.: Comparison of botulinum toxin injection and nerotomy in patiens with distal lower limb spasticity. Eu J Neurol, 15, 2008: 506–511.
28. Rowe, F.J., Noonan, C.P.: Botulin toxin for the treatment of strabismus. Cochrane Database Syst. Rev., 2012, Ef. 15:2: CD006499.
29. Růžička, E., Roth, J., Diblík, P.: Botulotoxin v léčbě blefarospazmu. Čas Lék čes, 131; 1992: 213–216.
30. Scott, AB.: Botulinum toxin injections into extra-ocular muscles as an alternative to strabismus surgery. Ophthalmology, 87; 1980: 1044–1049.
31. Scott, A.B., Kennedy, R.A., Stubbs, H.A.: Botulinum toxin injection as treatment for blefarospasm., Arch. Ophthalmol., 103; 1985: 347–350.
32. Vácha, J., Bodnár, M., et al.: Botulotoxín A – jedna z možností léčby strabismu. Folia Strabol Neuroophtalmol, 6; 2003, Suppl. 1.: 50–51.
33. Vartanian, A.J., Davan, S., H.: Complications of botulinum toxin A use in facial rejuvenation., Facial. Plast. Surg. Clin North Am, 11; 2003: 483–492.
34. Wabbels, B., Reichel, G., Fulford--Smith, A. et al.: Double-blind, randomized, parallel group pilot study comparing two botulinum toxin type A products for treatment of blepharospasm. J Neural Trans, 118; 2011: 233–239.
35. Winner, P.K., Sadowsky, C.H. et al.: Concurrent Onabotulinum toxin A treatment of cervical dystonia and concomitant migrace. Haedache, 18; 2012: 15 - 26.
36. Wojno, T.H.: Results of lacrimal gland botulinum toxin injection for epifora in lacrimal obstruction and gustatory tearing. Ophthal Plast Reconstr Surg, 27; 2011: 119–121.
37. Yoon, J.S., Kim, J.C., Lee, S.Y.: Double-blind, randomized, comparative study of Medoxin versus Botox in the treatment of essential blepharospasm. Korean J Ophthalmol, 23; 2009:137–141.