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

**SUMMARY**

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**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, there were surgically treated three patients after repeated applications of botulotoxine A derivatives. 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 derivatives.

**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 derivatives 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


**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 synaptic membrane of the neuromuscular junction. The process takes place in three phases: the pre-condition 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 Kern 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 therapy 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 (Bo-
tox®) from the Allergan company in the late 1980s, in 1990 there appeared
Abobotulinumtoxin A (Dysport®) from the Porton Down company, which la-
ter changed its name to Speywood. Further preparations are Incobotuli-
umtoxin A (Xeomin®) from the Metz Pharma company and licensed prepa-
ations on the basis of the above-na-
momed derivatives of botulinotoxin A: Azzu-
lure® (Ipsen Ltd.), Reloxin® (Ipsen Pharma) or Meditoxin® (Medi-Tox).
The basis of all of the above prepara-
tions is Clostridium botulinum type A
toxin – haemaglutinin complex, and as a result there is no significant difference
between the effects of these injected pharmaceu-
ticals [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 Vin-
hrady between 2006 and 2008. Deri-
atives of botulinotoxin A were repeatedly applied to the affected areas or clo-
sest surrounding areas on the three adult patients sent for treatment. In all of these cases the derivate concerned was Abobotulinumtoxin 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 condi-
tion of anamnestically indicated bila-
teral blepharospasm persisting for 15
years, which was diagnosed and trea-
ted in a neurological centre outside of
Prague. A total of 140 IU (= internatio-
nal 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 di-
rect connection with the application of Dysport. Although the condition was transitional, it gradually intensified. As a consequence the result was unsa-
satisfactory for the patient, since the resulting bilateral ptosis necessitated backwet tilting of the head.

Upon the first outpatient examination at the Eye Clinic of FH(University Hos-
pita)K 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 tre-
mor of the eyelids were determined, but not the classic image of blepha-
rospasm with an image of spasms (fig.
1). After spontaneous pacification the
width of the palpebral apertures was
2-3 mm (fig. 2), the margopupillary dia-
meter 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. Bilate-
ral 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 aper-
tures had a width of 7 mm and the mar-
gopupillary 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 administe-
red 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 amblyo-
pia accompanied by a divergence ex
anopsia. Over the course of 3 appli-
cations from June 2003 to November
2005, 100 IU was always administered
into the lower eyelid in five points.
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 adminis-
tration of Dysport was longer, from Oc-
tober 2003 to June 2006, in total 120
to 160 IU was always applied to both
lower eyelids of the patient in four po-
ints in eight sessions. The resulting
effect was a persistence of entropium of the lower eyelids, since after injec-
tion of the neurotoxin the patient did
not record a permanent effect or even
a significant temporary improvement.
In both patients a classic picture of
involvement 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. Ad-
justment 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 plas-
tic operation of the lower eyelid with
myrth cutting of the skin and subcutis
down to the orbicularis muscle, which
underwent partial resection in the sur-
face 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 mon-
ths 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 po-
sition 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).
DISCUSSION

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

ry 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 botulotoxin 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 blepharospasm [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 spas tic 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-ophtal-
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 botulotoxino 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.

CONCLUSION

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 derivate 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 derivate 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]. 

Pathological-histological analyses of the side effects of derivate 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-s triated 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.

LITERATURE


