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Botulinum Neurotoxin: Clinical and Cosmetic Use.

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ABSTRACT

Botulinum exotoxin (BoNT) is a neurotoxin produced by bacteria of the genus *Clostridium*, type C. botulinum. They cause botulism. The toxin causes inactivity of muscles or glands by blocking the release of acetylcholine from cholinergic nerve endings. the aim of the study is to present the clinical and cosmetic use of botulinum neurotoxin In the study has been used documentary method, with more than thirty scientific publications from medical journals from Europe, North America, Asia and others. Botulinum neurotoxin is the strongest known biological poison, but in same time, is an effective therapeutic agent in many fields of medicine. Its adjustment action with higher efficiency is used in strabismus, dystonia, diseases of the urinary system, hyperhidrosis, migraine, multiple sclerosis, Parkinson's disease, cerebral palsy and others. The appearance of facial wrinkles is mainly due to skin aging but some wrinkles and unaesthetic facial expressions are a result of overactive facial muscles. Success in application of BoNT as a selective depressor of the activity of skeletal muscles leads to widespread use in smoothing wrinkles. On the world market there are a variety of products containing BoNT for cosmetic purposes, which received regulatory approval or are under development. According to several studies the application of BoNT is distinguished by high efficiency and safety. Side effects are rare and reversible.

Keywords: botulinum neurotoxin, therapeutic effectiveness, cosmetic use, bacterial toxins

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INTRODUCTION

Botulinum neurotoxin (BoNT) is the strongest biological toxin known to mankind. It is produced by spore-forming anaerobic bacteria *Clostridium botulinum*, which causes botulism [3, 16].

There are eight antigenically distinct serotypes of BoNT - A, B, C1, C2, D, E, F, G [28]. Their action is to prevent neuronal transmission by blocking the release of acetylcholine (main neurotransmitter in the neuromuscular junction) and to cause muscle paralysis.

After several findings of successful use of BoNT in animal experiments, it was first administered to human in 1980. The toxin can be used for involuntary and uncontrollable muscle contractions, hyperactive glands and others. In cosmetic practice it has become one of the most desirable aesthetic corrections worldwide.

MATERIALS AND METHODS

In the study has been used documentary method, with more than thirty scientific publications from medical journals from Europe, North America, Asia and others.

THERAPEUTIC USE OF BOTULINUM NEUROTOXIN

BoNT has an important role in therapy of variety of disorders, and the list of new indications is rapidly expanding.

Strabismus – The injection of BoNT in the antagonist of the paralyzed eye muscle causes a temporary paralysis and balances eye muscles. After releasing of the acquired and the induced muscle paralysis, normal mobility of the eye is restored [22].

Hyperhidrosis - BoNT-therapy is highly effective non-invasive procedure for this condition [15]. Three to seven days after administration of BoNT the excessive sweating is usually overcome [6].

Focal dystonia - Studies show that BoNT-products not only reduce the abnormal movements and contractions, but also prevent secondary muscle degeneration [4, 19, 31].

Incontinence due to bladder pathology - The toxin is injected into the bladder wall to reduce the activity of the nerves that causes the incontinence. The therapy affects frequency of voiding and controls symptoms of the condition [12].

Chronic pain - BoNT influences migraine [9], chronic tension headache [30], masticatory myalgia, chronic neck pain and trigeminal neuralgia [4, 9].

Other uses - BoNT-products can be used with high efficiency in muscle spasms of wrist and hand in stroke-survivors, in gastrointestinal disorders [14], in hypersalivation and in chronic anal fissures [1]. They are effective in the treatment of hyperactivity of smooth muscles, eg. achalasia [28], allergic rhinitis [2], stammer [7] and bruxism [4].

Promising studies have been carried with children with cerebral palsy [34] and multiple sclerosis patients.

COSMETIC USE OF BOTULINUM NEUROTOXIN

Facial wrinkles appear mainly during skin aging but some wrinkles and unaesthetic facial expressions may result due to overactive facial muscles. The injection of strictly controlled dose of BoNT reversibly paralyzes selected muscle groups, temporarily reduces their activity and leads to visible smoothing of wrinkles [10]. The muscle is only partially paralyzed and normal movement is usually retained.

BOTULINUM NEUROTOXIN-CONTAINING PREPARATIONS

A variety of BoNT preparations is currently presented on the world market (Table 1). Nowadays, Botox® gives a share of 85% of the global market of products containing BoNT, as well as it is involved in most of research studies in the field [9].

Botox® and Dysport® are botulinum toxin type A preparations, but are quite different from each other – bacterial strain, preparation, diffusion and testing of efficiency. Recently it has been shown that a unit of Botox® is three times stronger than unit of Dysport® [29], but in contrast to Botox®, Dysport® can be stored at room temperature [28].

Xeomin® contains BoNT-A and is purified of all accessory proteins. There are numerous studies about differences in safety and efficacy between Botox® and Xeomin®. In fact, Xeomin® is a preparation without unnecessary proteins and its purer formulation has been suggested to lead to greater efficacy with reduced risk of sensitization or antibody formation [20]. However, its clinical significance has not yet been determined [36].

Myobloc®/NeuroBloc® is the only available botulinum toxin type B (BoNT-B) product. The clinical effect (in correcting glabellar wrinkles) of Myobloc® is shorter than Botox® [20] [33], but Myobloc® exhibits a faster onset of action and has a large area of diffusion [13]. Adverse effects are mild-to-moderate, transient and appear only at higher doses [9].

Global market offers other BoNT-containing preparations, but with limited application (mainly in Asia) – Prosigne®, Lantox® - CBTX-A; Neuronox® - BONTA. Others are in process of registration and approval (PurTox®).

Table 1: Comparison of botulinum toxin preparations [5, 9, 18, 21, 24, 25, 28, 36]

	Onabotulinum-toxin A	Abobotulinum-toxin A	Incobotulinum-toxin A	Rimabotulinum-toxin B
Commercial names	Botox®, Botox Cosmetic®, Vistabel®, Vistabex®	Dysport®, Reloxin®, Azzalure®	Xeomin®, Bocoture®	MyoBloc®, NeuroBloc®
Company	Allergan Inc. (USA)	Medicis Pharmaceutical Corp. (USA) - Reloxin®; Ipsen Biopharmaceuticals Inc. (France) - Dysport®, Azzalure®	Merz Pharmaceuticals (Germany)	Solstice Neurosciences Inc. (WorldMeds LLC) (USA)
Serotype	A	A	A	B
Active substance (molecular weight)	BoNT-A complex (900 kD)	BoNT-A complex (500-900 kD)	BoNT-A complex (150 kD), without accessory proteins	BoNT-B complex (700 kD)
Indications	Botox Cosmetic® - glabellar lines; Botox® - blepharospasm, cervical dystonia, strabismus, chronic migraine, hyperhidrosis, urinary incontinence	Blepharospasm, cervical dystonia, glabellar lines	Blepharospasm, cervical dystonia, glabellar lines	Cervical dystonia, glabellar lines
Countries	Over 75 countries around the world, including USA and Canada	Over 65 countries, including USA, Canada, Russia	USA, Germany and other European countries, Mexico, Argentina	USA, Germany and other European countries

EFFECTIVENESS AND SAFETY

According to several studies the application of BoNT is distinguished by high efficiency and safety [6, 8, 11, 27, 28, 32] and is associated with a high degree of satisfaction in patients and physicians [17, 19].

A study conducted by Sattler et al. (2010) shows that the application of BoNT for correction of glabellar wrinkles has reached 95.7% (onabotulinumtoxinA) and 96.4% (incobotulinumtoxinA) of satisfaction among patients and specialists [32].

Side effects are rare and reversible. They mainly consist of mild pain and local swelling at the injection site, diplopia (double vision) [17], redness, transient numbness, weakness in the neck, headache, malaise, dry mouth or nausea. The registered side effects calm down with increasing the distance from the injection site, although toxin migration to near muscles and other tissues is possible. The most serious adverse effects are temporary weakness (paralysis of nearby muscles), temporary ptosis of the upper eyelid and forehead (1-3% of patients)

DURABILITY OF THE EFFECT

The paralytic effect, after injection of BoNT has an average duration of three months. To maintain the efficiency, additional doses of BoNT are required at regular intervals. They depend on the initial dose and individual sensitivity. Most patients, treated with BoNT, require multiple injections over many years.

CONCLUSION

With more of 25 years of active use in therapeutic practice, BoNT is still one of the discoveries which continues to evoke scientific interest. Its use for medical and aesthetic purposes is expanded and improved every year. The effectiveness of the toxin in the treatment of cerebral palsy [23, 35], as an alternative to sphincterotomy in patients with chronic anal fissures [1] and in urological disorders [26] is actually under research.

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