Botulinum toxin in the treatment of strabismus

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Abstract

Introduction: Strabismus is an oculomotor imbalance that occurs in 0.5 to 5% of the population. There are various etiopathogenetic theories and several modalities of treatment. One of these modalities is the application of botulinum toxin intramuscularly. This chemodenervation causes temporary muscle paresis which acts as a recession while its antagonist contracts. This achieves a temporary correction of strabismus. However, further research is needed. The aim of the paper was evaluation of published research studies on botulinum toxin as a treatment option in strabismus, as a primary and adjuvant therapy and as a preventive therapy in patients with abducens nerve palsy.

For this purpose, we searched the major databases of the medical publications Medline and Pubmed, using keywords: strabismus, botulinum toxin. We found more than 50 articles related to our search for the last 30 years, 30 of which have been used for this review. In this review paper we have presented the most important insights from the literature, as well as our opinions and insights on the topic. Although further studies are needed regarding dosing as well as avoiding side effects, botulinum toxin has been shown to be a good alternative and adjunctive therapy to strabismus surgery, with the downside being that the effect is temporary. Positive effects and faster recovery have also been shown in patients with abducens nerve palsy.

Keywords: strabismus, botulinum toxin, esotropia, exotropia, abducens nerve palsy

Introduction

Strabismus is an oculomotor imbalance that can be intermittent or constant. It is a common condition that occurs from 0.5 to 5% of the population and up to 50% in special populations such as those with cerebral palsy. Strabismus is not only a cosmetic defect, but also has a huge number of negative effects, such as binocular vision disorders and stereopsis, and a negative impact on the patient's self-confidence and interpersonal relationships (Rowe and Noonan, 2017; Sharma et al., 2017).

Various theories have been proposed in the past to explain this disease, ranging from muscle theories supported by Scobee (1948) to classical reflexogenic theories. Chavasse suggested that abnormal visual input may inhibit the development of binocular fusion leading to strabismus. Advances in imaging technology and genetics have altered previous views. High-resolution magnetic resonance imaging has led to the detection of extracocular muscle "pulleys" that represent condensation of connective tissue in the posterior tenon fascia. They are thought to help maintain the direction of action of the extracocular muscles. Heterotropia or abnormalities of the "pulleys" can lead to
the development of strabismus. The instability of the rectus “pulleys” has been shown to be associated with incomitant strabismus (Oh et al., 2002; Scobee, 1948; Sharma et al., 2017).

Apart from the etiology, changes also occur in terms of treatment modalities. New surgical techniques are introduced, as well as non-surgical pharmacological modalities. One of the methods that have been tried in the past, and started with Alan Scott in 1980, is the intramuscular injection of botulinum toxin (Scott, 1980).

Botulinum toxin (BT), an exotoxin of the bacterium Clostridium botulinum, was approved by the Food and Drug Administration (FDA) in 1990. It acts on the level of acetylcholine and results in muscle weakness or paralysis 3 to 5 days after injection. Muscle paralysis lasts approximately 8 to 12 weeks (Cole and Camuglia, 2012). The chemodenervated muscle lengthens and its antagonist contracts. This temporary paralysis of the injected extraocular muscle affects the ocular balance, thereby leading to balancing of the visual axes which in turn allows binocular vision. Botulinum toxin can also be used as adjunctive therapy in strabismus surgery (Scott, 1980).

Description of evidence

We searched the major databases of the medical publications Medline and Pubmed, using keywords: strabismus, botulinum toxin. We found more than 50 articles related to our search for the last 30 years, 30 of which have been used for this review.

The use of botulinum toxin in ophthalmology: indications, mechanism of action, contraindications and complications

There are seven known botulinum toxin serotypes (A, B, C1-2, D, E, F, and G) isolated from the bacterium Clostridium botulinum (Pirazzini et al., 2017). The use of botulinum toxin in ophthalmology can be classified into several categories: eyelids, strabismus, cosmetics and others. In eyelid disease, it can be used to treat blepharospasm, hemifacial spasm, eyelid opening apraxia, or to cause ptosis in eyelid retraction conditions or exposure keratopathy. In cases of strabismus, it can be injected into a muscle joint to induce paralysis. For cosmetic purposes, it can be used to relax facial muscles to reduce wrinkles, while other indications include treatment of chronic dry eye, lacrimal hypersecretion, and pain relief in an acute angle-closure glaucoma attack (Teo and Chee, 2012). The release of the neurotransmitter acetylcholine into the synaptic cleft requires the participation of a vesicle-associated membrane protein (synaotosomal protein-25 (SNAP-25)), which forms a vesicle-associated syntaxin protein complex. After intramuscular injection of botulinum toxin, the molecule undergoes endocytosis at the neuromuscular synapse. Furthermore, it binds to the protein complex, thereby inhibiting the release of acetylcholine. Consequently, the transmission of nerve impulses through the synaptic cleft to the end plate of the motor muscle is interrupted, i.e. it is paralyzed (Pirazzini et al., 2017). Injected muscle paralysis begins between 48 hours and 5 days and lasts clinically for at least 5-8 weeks. Recovery of muscle function takes 5 to 14 weeks, depending on the density of the innervation, the injection site, the amount, and the concentration of the solution (Vissenberg et al., 1993). Treatment with botulinum toxin causes pharmacological recession of the injected extra ocular muscle, i.e. the paralyzed muscle is elongated, while its agonist is contracted (Gómez de Liaño, 2019).

Most studies that have investigated the action and efficacy of botulinum toxin as a treatment for strabismus considered the possibility of treating strabismus in children as the primary treatment for strabismus; in children who need reoperation; in adults to improve the effect of surgery and reduce the chances of failure; in patients with abducens nerve palsy and as adjunctive therapy in classical strabismus surgery (Rowe and Noonan, 2017). The main indications for botulinum toxin injection are: esotropia or exotropia with small to moderate angle deviation (<40 prism diptors); acute esotropia with acute onset; postoperative residual or subsequent strabismus (2-8 weeks postoperatively or later); acute paralytic strabismus to relieve diplopia while the paralysis resolves (mainly sixth nerve palsy, sometimes fourth nerve palsy); active thyroid disease (Graves’ disease); presbyopic eyes, when surgery is not recommended; as adjunctive surgery for large-angle esotropia or sixth nerve palsy or for large-angle exotropia (Hered, 2018; Ozkan et al., 2006). According to the results obtained in review by Rowe and Noonan (2009), the therapeutic use of botulinum toxin in strabismus is ranging from a lack of evidence for a prophylactic effect of botulinum toxin in acute sixth nerve palsy to a poor response in patients with horizontal strabismus without binocular vision, to no difference in response in patients requiring re-treatment for acquired esotropia or infantile esotropia (Rowe and Noonan, 2009).

The most commonly declared contraindications for botulinum toxin use in strabismus treatment listed in several studies are unrealistic expectations, neuromuscular disorders such as amyotrophic lateral sclerosis (ALS), myasthenia gravis, Eaton-Lambert syndrome, an autoimmune disease that affects neuromuscular connection in patients with progressive external ophthalmoplegia in both pregnancy and lactation (Tan et al., 2013; Tinley and al., 2010; Qureshy and Marechek, 2017).

Additionally, ecchymosis, pain or infections have been reported as most common complications presented as local effects, whereas ptosis, diplopia, lagophthalmos, facial weakness, and dry eyes are complications defined as dysfunctions (Teo and Chee, 2012). The rate of complications when using botulinum toxin in strabismus treatment ranged from 24 to 55.54% in the study of Rowe.
And Noonan (2009). And more recent study from 2017 listed the following complications as most common, ptosis (from 9 to 41.66%) and vertical deviation (from 8.3 to 18.51%). Ptosis has also been reported to occur less frequently when botulinum toxin treatment has been combined with sodium hyaluronate in comparison with isolated botulinum toxin used as single treatment (Rowe and Noonan, 2017).

Regarding the doses of botulinum toxin applied for strabismus treatment there are observed variations ranging between 2.5 and 5 U, doses that are below the toxic doses of botulinum toxin (Chrouch, 2006). The literature evaluation suggested that the initial doses of botulinum toxin for individual muscles were originally proposed by Alan Scott. For horizontal and vertical deviations under 20 prism diopeters (PD), for adults over 12 years, the doses are from 1.2-2.5 units, and for children up to 1.25 units. For larger horizontal and vertical deviations, the dose is increased depending on the age and body weight of the child. For nerve abducens paresis lasting more than one month, the dose for adults is from 1.25 to 2.5 units, and for children up to 1.25 units (Scott, 1990). The dose is adjusted according to the patient’s age, size of the deviation, refractive error, and type of strabismus. Some authors suggest when applying botulinum toxin to children under 3 years of age: 2.5 U in the dominant eye and/or 2.5 U (if the deviation is < 30 prism diopeters, PD) or 5 U (if ≥ 30 PD) in the non-dominant eye. In children from 3 to 10 years: 2.5 U in the dominant eye and 5 U in the non-dominant eye, 1.5 U for the upper rectus muscle, 1.5-2.5 U for the lower oblique and lower rectus muscles, 3-5 U for medial or lateral rectus muscle and 10 U Botox in the presence of fibrosis (BOTOX® Prescribing Information, 2021; Dressler, 2004).

Published results

There are numerous studies investigating the effect of botulinum toxin as a possible alternative to surgery. It is considered to be used as a treatment for horizontal and vertical strabismus, nystagmus, dissociated vertical deviation, sensory strabismus, ophthalmoplegia, and paradoxical diplopia (Crouch, 2006). According to the Rowe and Noonan, the achievement of this treatment approach is classified with primary and secondary outcome. Improved ocular balance and reduction of the deviation angle measured with prisms or synoptophore, in a monitoring period of six months, are considered as primary outcomes. Secondary outcomes include achievement of binocularity: cover test, motor fusional vergences and stereo vision. As a successful outcome, is considered when the complete control of the deviation angle in the range of 10 PD from ortho position, with normal parameters for binocular vision is obtained. The results with reduction of the deviation in the range of 20 PD from ortho, with binocular vision (group A), and reduction of the deviation within 20 PD, without binocular vision (group B), were considered less successful (Rowe and Noonan, 2017).

Benabent et al. (2002), studied 40 children with essential infantile esotropia. The children were injected with 7 IU of botulinum toxin in the medial rectus without electromyographic monitoring. The average initial deviation was 25.8 PD, to be reduced to an average of 8.5 PD 6 months after injection (success rate 53%). Ptosis was a complication in 23% of injected eyes, which was temporary and lasted less than 3 months in all patients.

Campos et al. (2000) evaluated the results of botulinum toxin performed under direct "open sky" visualization in 60 children with essential infantile esotropia. The average age at injection was 6.5 months. The average follow-up was 5.2 years and the success rate was 88% per treatment. All patients developed transient exotropia 1 to 2 weeks after the procedure. A total of 20% of all injected eyes developed transient ptosis.

In 1994, McNear et al., reported the results of 57 patients monitored for an average of 12 months. The authors analyzed two subgroups according to age in which botulinum toxin injection was performed. A dose of 2.5 IU botulinum toxin was injected guided by an electromyographic monitor. Both subgroups (before and after 12 months of age) had 100% success in adjusting the alignment (McNear et al., 1994).

In study of 13 patients, 6 with idiopathic orbital inflammatory syndrome (IOIS) including myositis, 3 with previous fractures of the orbital wall, 1 with a post-Schwannoma optic resection, 1 with lymphoma, 1 with metastasis, and 1 with post-hemorrhage of the upper ophthalmic vein, botulinum toxin has been applied on the lower rectus. The average follow-up of 14 months has confirmed favorable effect in 9/13 (69%) patients and resolution was present in 4/6 (67%) patients with IOIS. The obtained results confirmed that vertical strabismus, which is secondary to a number of orbital conditions, especially inflammatory ones, can be successfully managed with botulinum toxin injections into the lower rectus (Bunting et al., 2013).

In 1999, Tejedor and Rodriguez, conducted a randomized study of 55 children with infantile esotropia who underwent retreatment with two different procedures, reoperation or application of botulinum toxin. The results have confirmed that botulinum injection was a rapid and less invasive alternative to reoperation in children who had been unsuccessfully treated with infantile esotropia correction surgery (Tejedor and Rodriguez, 1999).

Lee and colleagues conducted a study of 54 participants in 1994 with acute unilateral sixth nerve paresis in two groups: one group received ipsilateral botulinum toxin (Dysport) and the other group recovered without any treatment. Achieving complete normal ocular motility and complete binocular vision was considered as complete recovery. Normal binocular vision and minor asymptomatic defects or minor asymptomatic vertical
deviation was considered as stable recovery. Persistent esotropia in the primary position and diplopia was considered as non-recovery. The control group had a final recovery rate of 80% and the injected group had a final recovery rate of 86% and no serious side effects were reported. The results have suggested that there was no evidence of a prophylactic effect of botulinum toxin in the study group (Lee et al., 1994).

Carruters et al. (1990), conducted a study of 30 adults with esotropia or exotropia without binocular function, with two treatments, one group with botulinum toxin and the other with surgery. The groups were compared for a degree of deviation less than or equal to 10 PD. Patients were followed for six months. In the botulinum-treated group, those patients with an initial deviation of 20 PD or less showed better results than those patients with a deviation greater than 20 PD. Patients with esotropia showed 88.89% change with surgery and 51.55% change with botulinum toxin treatment. Patients with exotropia had 95.83% change with surgery but 50.3% change with toxin treatment. Due to the small number of patients included in the study, 20 patients with esotropia and 10 patients with exotropia, in order to obtain more formal comparison larger studies are required (Carruters et al., 1990).

In 2012, Minguni et al., in a randomized study of 23 adults, compared the effect of combined therapy, surgery plus botulinum toxin in one group, and placebo (hyaline solution) surgery in the other group in patients with concomitant esotropia and exotropia. The 12 months follow-up suggested that, although initially the effect was pronounced in the botulinum toxin group, that effect did not last longer than three months. In two other studies by the same author, the transient effect of botulinum toxin was emphasized (Minguni et al., 1990).

In 2013, Chen et al., studied botulinum toxin as the first treatment option for 47 participants with infantile esotropia. Participants were divided into two groups, the first receiving botulinum toxin together with sodium hyaluronate and the second group receiving botulinum toxin as single treatment. After the followed up two weeks, three months and six months after application, the results showed that injections of botulinum toxin, in combination or without sodium hyaluronate, in the absence of electromyography, are affective and feasible for treatment in infantile esotropia. Additionally, in the group where botulinum was given with sodium hyaluronate, the degree of ptosis as a complication was slightly lower than in the group with isolated botulinum toxin (Chen et al., 2013).

**Conclusion**

The positive effect of botulinum toxin has long been used in ophthalmology and strabismus is an area where it finds application. Despite the temporary effect, it has proven to be a good alternative as a primary treatment, and even better as an adjunctive therapy along with surgical treatment. Although the dosage is not standardized, the most commonly used doses ranged between 2.5 to 5 units, which is below the toxic dose. The effect of pharmacological recession on injected muscle lasts up to 8 weeks. It can be used as a good prophylactic therapy in abducens nerve palsy, as well as in orbital diseases with involvement of the inferior rectus, which reduces vertical diplopia.

**References**


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Резиме

Ботулинум токсин во третман на страбизам

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Ключни зборови: страбизм, ботулинум токсин, езотропија, езотропија, абдукценс пареза

Страбизмот е пореметување на окуломоторната рамнотежа, кое се јавува кај 0.5 до 5 % од популацијата. Постојат различни етиопатогенетски теории и неколку модалитети на третман, од кои еден кој е сеуште во фаза на истражување е апликацијата на ботулинум токсин интрамускулно и предизвикување на привремена пареза на мускулот, што делува како рецесија, додека неговиот антагонист се контрахира. Со ова се постигнува привремена корекција на страбизмот. Целта на овој труд беше да се истражат досега направените студии за ботулинум токсин како третманска опција кај страбизм, како примарна и како адвувантна терапија и како превентивна терапија кај пациенти со пареза на абдукценс. За таа цел ги пребаравме поголемите бази на податоци за медицински публикации Макед. фарм. бит., 68 (1) 3 – 8 (2022)
Medline и Pubmed, со внесување на ключните зборови: страбизам, ботулинум токсин. Добивме повеќе од 50 статии во врска со нашето пребарување, за последните 30 години, од кои 30 послужија за овој преглед. Во овој прегледен труд ги прикажавме најважните согледувања од литературата, како и нашите согледувања од истражувањето во оваа насока. Иако се потребни дополнителни студии во однос на дозирање, како и избегнување на несаканите ефекти, сепак ботулин токсинот се покажал како добра алтернатива и адјувантна терапија на хируршкиот третман на страбизам, со негативна страна што ефектот е привремен. Позитивни ефекти и побрзо закрепнување се покажало и кај пациентите со пареза на абдуценс.