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APPLICATION OF BOTULINUM TOXIN IN FACIAL PARALYSIS: A REVIEW STUDY

Beatriz Brumato Macedo[1], Rogério Rodrigo Ramos[1,2*]

[1]Universidade Brasil (UB), Fernandópolis, SP, Brazil
[2]Centro Universitário de Santa Fé do Sul (UNIFUNEC), Santa Fé do Sul, SP, Brazil

*Corresponding author:
E-mail address: rogerio.enfer@gmail.com tel. +55 17 34654200

ABSTRACT

Botulinum toxin (BT) considered a potent substance with high potential in several treatments, has also been gaining space in dental clinics for the treatment of various pathologies, is safe when used in appropriate doses and contraindications are respected. Before starting BT therapy, it is necessary to communicate the patient about all the potentialities and limitations of treatment. The toxin has become an efficient option for the treatment of facial paralysis (FP), a pathology that causes contraction in the facial muscles, causing temporomandibular dysfunction, damage to the process of eating food and liquids, as well as aesthetic constraints, compromising the patient's quality of life. The objective was to present the application of BT as a therapeutic option in FP. This is a review with qualitative data researched in PubMed, VHL, SciELO and LILACS. Seventy-two studies were found, excluding 27 that were outside the inclusion criteria, and 45 studies were selected. It was found that the first step to its use is to analyze the patient, evaluating the facial resuscitation procedure, defining the possibility of reversal or considerable improvement. Subsequently, it is essential to determine the cause of paralysis, its duration and the functional deficits that the patient presents, after establishing the cause, its indication is evaluated. It is essential that an individualized evaluation is always performed, proposing a realistic therapy, and making the patient aware that it is a temporary treatment. The medical literature also shows a positive effect for the use of BT in the treatment of FP, improving the quality of life, especially the patient's self-esteem.

Keywords: Facial paralysis, Facial nerve, Botulinum toxin.

1. INTRODUCTION

Peripheral Facial Paralysis (PFP) can be conceptualized as a condition of immobility, caused by the exhaustion of the facial musculature, which causes aesthetic limitations to the patient, thus compromising the patient's quality of life. Thus, it is always very important to be attentive to any therapy that can mitigate pathological complications and aesthetic inconveniences to the patient[1].

The procedure to treat facial paralysis (FP) with botulinum toxin (BT) involves infiltration with insulin needle or intramuscularly of small amounts of diluted BT with saline directly into the affected facial muscles. Once prepared, the solution should be administered before 4 hours and during this time should be in the refrigerator. The dose of BT used is 2.5 Units (U) per infiltration point. Treatment is performed during outpatient consultation[2].

BT, or known as Botox, is a drug obtained from the bacterium *Clostridium botulinum*. It acts on the motor plate (connection of the muscle fiber with the motor neuron) preventing the release of the neurotransmitter "acetylcholine", such a substance that brings the message of transmission of the central nervous system (CNS) to the skeletal striated muscle. BT is an important part of the treatment of FP, using it to reduce the tone of the shaken muscle, achieving a reduction in pain and thus improving the patient's quality of life[3].

Although its use is used for facial aesthetic treatments, BT has also been used in dentistry in a therapeutic way in several pathologies, such as bruxism, temporomandibular dysfunction (TMD), facial asymmetry, gingival smile, pain symptoms, as well as success rates for the treatment of FP. Due to the anatomical knowledge acquired by dentists (CD), during their professional lives, they easily know the anatomical supports of the head and neck, becoming able to perform treatments of the oral cavity and face, in a safe and conservative way, so it is advisable to be made by trained and trained professionals[3,4].

Among the most used types of BT type A, who have shown considerable success rates in the use in the procedure of patients with FP that can be either unilateral or bilateral, provoked by numerous reasons such as: stroke, traumatic and surgical injuries, paralysis of undetermined etiology, did well viral and bacterial infections, developmental anomalies that cause asymmetry in the face, nervous changes in muscle, which most causes negative impacts on the patient's life. The use of BT in the dental area causes some divergences among scholars, however, constant research proves the efficiency of BT use in the therapy of these disorders[5]. In the context, the present objective of this study was to present the use and application of botulinum toxin as a therapeutic option in facial paralysis.

2 METHODOLOGY

The work refers to a literary research, where three databases (SciELO, VHL, LILACS and PubMed) were chosen for the research. As a search strategy, the following descriptors were adopted: Facial paralysis, Facial Nerve, Botulinum Toxin and "E" was used as boolean operator.

Inclusion criteria were articles published in international and national journals, in English and Portuguese, with description of botulinum toxin as a therapeutic measure in facial paralysis. Studies that were not in accordance with the proposed theme were excluded.

For the selection of articles, the data were analyzed by the qualitative approach found in the titles and abstracts, thus, 72 articles were found for the review, being submitted to eligibility analysis and, later, 45 studies were selected for careful evaluation (Figure 1).

The risks of bias of the selected articles were evaluated for systematic errors or limitations in the design of the research, therefore, articles with discrepancies found in the abstract, in the body of the text and articles that did not present a conflict of interest were excluded.

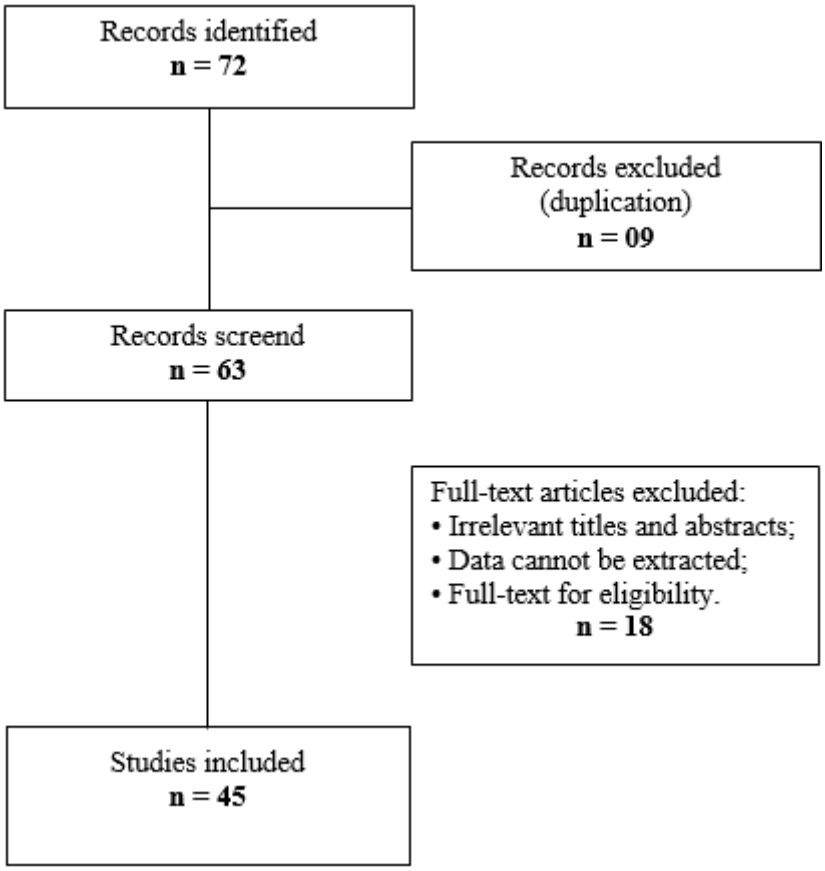

Figure 1. Flowchart.

3 LITERATURE REVIEW AND DISCUSSION

3.1 Main Approaches to Facial Palsy

PFP also known as Idiopathic Facial Palsy (IFP) is also called cryptogenetics, frigor, rheumatic, or Bell's palsy. It is a relatively frequent picture of varied etiology and evolution, its most common form is bell's idiopathic or idiopathic paralysis. Its incidence is around 20 to 30 cases per 100,000 inhabitants per year, accounting for an average of 70% of all cases associated with PFP, without significant differences in terms of race or geographic distribution. The occurrence is approximately the same in both sexes, and may appear at any age, although it is slightly more frequent in individuals > 65 years and rare in children < 15 years[6].

It is generally considered a benign pathology, although its recovery is variable and sometimes has the risk of leaving permanent sequelae that can go beyond purely cosmetic. Clinically it is equivalent to a paralysis of the entire musculature of the face, thus differing from the central origin, in which only the small amount of it is affected. The diagnosis of this disease, although excluding, is almost exclusively based on clinical findings. The procedure combines physical methods with other pharmacological methods (essentially corticosteroids), but sometimes they should also be supplemented with rehabilitative surgery and neuromuscular retraining[7].

The seventh cranial nerve (facial nerve) contains mixed motor fibers. Motor fibers are born from large multipolar cells of the facial nucleus and describe an arc around the abductor nucleus. Neurons from

which secret fibers form the upper salivary nucleus, and gustatory ones; these fibers are provided by an isolated nerve, intermediate nerve. Both parts of the nerve run through the internal auditory canal (internal acoustic meatus) to penetrate the facial canal or the fallopian aqueduct. The geniculate ganglion is located at the first angle of the nerve inside the cliff (external knee of the face). The facial canal runs over the tympanum box and is through which it leaves the skull (forame estilomastoide). Within the facial canal are born the following branches: a) large petrous nerve (secret pre-loglinic fibers for the lacrimal, nasal and palatine glands); b) stoering nerve (inherbs the homonymous muscle of the middle ear); and c) tympanum cord (flavor fibers of the two thirds preceding the tongue and preganglionic fibers of the sublingual and submandibular glands)[8].

Once the skull is abandoned, the facial nerve (FN) is broken down in its terminal branches at the height of the parotid gland (parotid plexus): I) posterior auricular nerve; II) branches for the posterior belly of the digastric and sylthene muscle; and III) parotid plexus with time, zygomatic, oral, cervical and marginal branches of the mandible. These nerve fibers instilled the entire imitative musculature[9].

Its mechanism probably consists of a change in microcirculation, which leads to hyperemia with the formation of an edema in the nerve bay, which, being in a bone canal with inextensible walls, undergoes a compression with ischemia that alters venous return and establishes a vicious cycle. PFP is a picture of acute or subacute establishment that is characterized by a flaccid paralysis of all muscles of the ipsilateral facial mimic, both upper and lower. Sometimes it can be preceded by a viral process. Paralysis is constantly followed by sensitivity to the modified palate due to tympanum cord binding and hyperacusis due to paralysis of the stirrup muscle. Occasionally ipsilateral otalgia sensory changes may occur. Another possible accompanying symptom is Epiphora, produced by the inability to lower the eyelid and drag the tear along the surface of the cornea, a fact that can influence the protection of the eyes, making the eye more susceptible to ulcers[8].

If symptoms occur gradually, within weeks or months, they do so bilaterally or partially, recurrent episodes occur, or there are no signs of recovery in two or three months, etiology that is not idiopathic should be suspected and secondary causes should be ruled out. The diagnosis of PFP is mainly based on clinical history and physical examination, sometimes aided by complementary tests, and should focus on the distinction between peripheral and central forms (Table 1)[10,11].

Table 1. Peripheral and central forms of facial paralysis.

Central	It is the one that is accompanied by hemiplegia on the same side, affects the voluntary movement of the lower facial muscles, preserving the frontal branch. In addition, emotion-reactive facial movements are usually normal. Among the most frequent causes are strokes, tumors and infections.
Peripheral	There is involvement of all three branches, i.e., loss of voluntary movement of all mimic muscles of the affected hemilate, alteration of lacrimal secretion and, in certain circumstances, hyperacusis.

Source: (CALAIS *et al*.[10]; TACON *et al*.[11]).

Being clear that it is a PFP, it is necessary to distinguish the idiopathic form (80%) from other secondary forms, mainly to establish a correct treatment and determine the prognosis. This will make you suspect that it is an idiopathic PFP your rapid establishment, less than 48h of evolution, exploration of the normal head, neck and ear and recovery of facial muscle mobility in a maximum of six weeks. On the contrary, it will lead to a possibly non-idiopathic PFP an establishment of the slow and progressive clinical picture, with the presence of spasms before paralysis, involvement of a single branch or bilateral involvement and lack of recovery in six weeks[8].

It is necessary to reinforce that FN can be reestablished at different levels to restore its function, but it will depend on what led to paralysis, also taking into account the type of injury, the age of the patient, the nutrition of the nerve in which there was neuromuscular involvement and the form where treatment should be based and individualized for each patient, in relation to the recovery period it is difficult to predict, but it can vary from weeks to years[12].

The consequences caused by FP can directly harm the patient's life, causing psychological problems due to their functional and aesthetic impairment, many people even obtaining a functional improvement also seek aesthetic improvement, because this influence on self-esteem is proven[13].

Driven by this reason, many professionals from various medical areas carry out constant studies and research to offer the best treatment for patients, a treatment that can contribute both in terms of health and social interaction of the patient[1].

3.2 The Mechanism of Action of Botulinum Toxin

In 1895 a bacteriologist known as Van Ermengem observed a Eurotoxic substance known today as BT, popularly called Botox or BoNTA, by many is recognized as one of the most intense and extremely important substances, not only in Brazil, but in the world for having a wide range of purposes and uses, effectively contributing to the areas of health and aesthetics. This substance is due to a process in which a bacterium is able to provide a protein that provides the neurotoxin, capable of causing a muscle relaxation at the site of its application. Some time after his discovery in 1950, Brooks disclosed his competence to promote muscle relaxation through acetylcholine blockage, which occurs in motor neurons, but it was only in 1980 that the first paper on the use of BT in humans for therapeutic purposes was published[14-16].

Another point that should be highlighted is the microbial agent "*Clostridium botulinum*". *C. botulinum*, found in marine environments or in soil anywhere in the world, Gram-positive anaerobic that can be seen in the form of spores, is responsible for the production of an efficient substance, originating from bacterial fermentation[17,18].

After several fermentation tests with *C. botulinum*, 8 serotypes were identified that have immunologically different characteristics, varying between themselves and in their potency because each has a mechanism of action and proteins found inside the cell, however regardless of the serotype, all of them are able to promote an acetylcholine blockade, are released in nerve endings, for some scholars the serotype is classified as the most potent among all being more studied in its therapeutic purpose, it was also the first to be created for clinical use. This without promoting any kind of alteration of the neural condition or synthesis and deposit of acetylcholine, serotype A, a neurotoxin that performs the impediment of the release of acetylcholine that happens in the nerve terminals of cholinergic synapses[19-22].

This inhibition and blockade of acetylcholine, occurs in several stages, in the first of these there is an inconvertible union to the receptors of the pre-syncatic membrane of the motor nervous terminal, which establishes a contraction of the muscles selectively, in the next step, then happens an endocytosis process, which causes the cytoplasm of neurons to promote the release of a part of the molecule, and in the end, the denervation of the muscles occurs functionally. If correctly applied, BT promotes, in the defined sites and in correct doses in the musculature, a partial stimulus of denervation, thus limiting muscle contraction without a definitive and complete paralysis[23,24].

As mentioned the effect of BT occurs through a process established in phases, being: the binding, internalization, translocation of the membrane and the activity of proteases, it is necessary that the toxin fully enter the nerve termination in order to be able to exert its effect and function. The connection will be performed by specific BT for cholinergic nerve terminals, being an irreversible connection, which will only be intercepted by the heavy chair, because the light chair is only responsible for promoting toxicity inside the cell[25-27].

The onset of BT action in tissues is quite variable, and may occur in some days taking up to 2 weeks to present its effect, with the duration of around 6 weeks being able to extend up to 6 months, the average is between 3 and 4 months, an average period that varies from patient to patient. In histological examinations it is possible to observe that in the period in which the toxin is presenting its effects more intensified, muscle atrophy occurs with a modification of muscle fibers. When the process of finalization of the effects of the toxin occurs the rehabilitation period, again occurring innervation, with a new formation of shoots and terminal plates with a smaller size, being allowed to reverse the paralysis generated locally[24-26].

It is necessary to reaffirm that each muscle needs an established dose for the application of the toxin to be done appropriately, and there is no application of a higher dose than recommended, because in these cases there is a risk of muscle weakness. Risk that can be enlarged to nearby muscles if introduced doses above indicated, risks and side effects that are mostly nonexistent, provided that the indications are obeyed. There is also a relationship between the dose of BT to be placed and the durability of the effects that are produced, however this is perceived only when the amounts applied are relatively low, only so it is possible to measure after 3 months of application the use of higher doses[28].

When the application of BT is performed on a high-activity muscle, the decrease in the muscle belly in which the toxin was applied is evidenced by the paresis that is induced. In cases of muscle hypertrophy caused by great activity during long periods, BT application can provide a return to size, this is normal muscle, which similarly occurs by paresis caused in the musculature[29].

When administering BT injection for an extended period of time, a real muscle atrophy may occur, however this consequence is not relative there is one of the mandatory effects of toxin administration, so it is an element that should not be considered to define the efficiency of the product[30].

3.3 Botulinum Toxin and its use in Dental Clinics

In the area of anthology, BT has become a way of choosing the treatment of various oral and facial pathologies, but it is of paramount importance to be aware of the protocol of its use, so that the application becomes effective and safe[29].

Due to its high efficacy, BT has been the therapy chosen for facial compensation of patients, who return to muscle activity, promoting facial symmetry, through a less invasive treatment, capable of providing better functional questions, about the patient's self-esteem and psychological conditions[31].

Studies prove that the use of BT presents satisfactory results in most treatments performed with it, however it is essential that the professional has adequate knowledge and training to perform the procedures[24].

In dental clinics throughout the country expired BT used for the blockade and conduction of nerve stimulation, reducing the potential of muscle contraction through the inhibition of acetylcholine, with significant increase, the CD has been using for the treatment of facial paralysis and asymmetries, hypertrophy of the masseter muscle, TMD, myascial pain, sialorohisis and aesthetic procedures, as a gingival smile, its application requires a deep knowledge of facial anatomy[32].

BT has a good tolerance and acceptable safety since it is manipulated under the conditions of the dentist, presenting some restrictions between them: pregnancy and lactation, patients over 75 years, allergy to the drug. Its use can bring some side effects being: edemas, erythemas, hypoesthesia and ecchymosis. Some rare patients may exhibit some resistance to BT therapy. In addition to aesthetic and functional improvement, studies also validate the improvement of facial spasms, which has been increasingly encouraging the use of this medication in dental clinics[33,34].

Complementary tests such as viral investigation and magnetic resonance imaging help to prove the etiology of FP, because it allows the identification of tumors and traumas through intravenous paramagnetic contrast, which is a real inflammatory in the various segments of FN, a detailed neurophysiological study contributes mainly to cases of bilateral paralysis, because through it it is possible to identify the degree of paralysis progress[35].

As previously pointed out, an expressive number of studies and research have been conducted on the use of BT and its application in the orofacial field, a broad purpose for several types of pathologies related to anatomical dysfunction or hyperfunction of the musculature, BT also has analgesic properties, important for the treatment and reduction of pain caused by bruxism[36,37].

As a therapeutic function, BT has been used since 1973 by Scott and collaborators in the treatment of strabismus. However, its field of activity was contemplated in 2019 by the Federal Council of Dentistry through resolution FCD-198/2019. Thus, it was released for the treatment of several pathologies, but the CD courses or specializations in the area, becoming fit and responsible for the aesthetic and functional procedure of the face in its patients. As a result, the CD should be aware of the anatomical structures of the head and neck and their anatomical variations, as well as license to treat diseases of the face and oral cavity[31].

BT is becoming increasingly popular, because it is not a surgical procedure, considered as minimally invasive and with high efficiency in the procedures of corrective and preventive applications of the facial area, since it causes immunological responses, with rapid recovery, this does not cause limitations of the patient's activities[38].

It can be affirmed that BT, when used as an auxiliary procedure, demonstrates considerable advances in the dental area. However, it is extremely important that protocols are individualised and strictly respected in each standard and in each indication[39]. This is because it is the only treatment with BT, it is the

responsibility of the dentist, after the evaluation of each point necessary for application, as well as its amount and possible complications, the aim is to avoid difficulties and reduce any side effect that may arise[3].

3.4 Treatment of Facial Paralysis with Botulinum Toxin

PFP therapy with the use of BT, aims at reducing or eliminating automatic, involuntary actions of the muscles of the face in the paralyzed region, reducing asymmetry and hyperfunction of the muscles is on the paralyzed or contralateral side. The possible result due to the ability that botulinum has inhibited the release of acetylcholine in motor nerve endings[38].

Botox treatment is safe because the amount used is what each muscle needs, without ever exceeding the maximum allowed dose. The toxin remains at the injected point for a long time and does not come into contact with sensitive organs such as liver, kidneys or heart. In general, treatment is not excessively painful. BT should be injected into hyperactive muscle (usually 1 to 4 injections per muscle). Injections can be unpleasant, although they vary depending on the tolerance of the patient[34].

There are no lasting side effects. A temporary decrease in the tone of a muscle located near the injected area (usually without interfering with its function) may occur. A small hematoma may also appear that disappears spontaneously in a few days[38].

As the treatment protocol is established individually for each patient, it is not possible to determine a specific protocol, but there is a standard dose parameter that can serve as the basis for therapies. This is necessary to compare this to the dose difference by points, that is, the muscle where it will be applied. To Shinn *et al*.[40] it has a difference of 2 to 3 biological U from one to each, with exemption from the platysma muscle that can reach up to 10 U. In addition to this muscle, the mouth orbicularis and lip lifter also require a greater amount of material.

It is possible to stop that some muscles that are compromised by FP need a greater amount of BT in order to respond to the expected result[1].

In other studies, different amounts of toxin per point of application, infiltration of 1.5 to 2.5 U on the static side and 2.5 to 5 U contralateral were found. Three sessions of toxin application are required in doses of 1.5 to 3 U/muscle. Some studies also report the use of the toxin in the different phases of FP, in the most acute phase between 24 and 48h after the occurrence of paralysis, doses ranged from 1 to 4 U/muscle on the contralateral side and the application should be repeated after four months. In a chronic phase, comprising about 8 months after paralysis, dose between 1 to 1.5 U/muscle on the affected side and contralateral side, however, doubling the dose at each point. Proving that in all phases there was a significant evolution after the application, proving the benefits of BT use[5].

Improvement in symmetry and motor capacity of PFP patients used as BT therapy has also been proven. There have also been reports that patients have seen a considerable decrease in mouth bites on the paralyzed side. Thus, the improvement of the patient's quality of life by reperforming the movements of the face, but coordinated and with balance of the contralateral side. BT is being considered as a new therapeutic option that presents less traumatic conditions than surgical interventions and with immediate post-outcome[1].

In the study of Remígio *et al*.[41] different formulations were evidenced for the preparation of type a serum among them: Onabont, Incobont and Abobont, and only the way of use was changed, respecting the amount of biological units for each formulation, it was evidenced that Abobont caused muscle weakness more frequently after injections, a side effect of hypersalivation was also observed, however, there was an improvement in speech understanding and symmetry, in addition to a moment of confidence that was reported by patients which establishes more benefits than harm.

In the work of Shinn *et al*.[40], it was observed that the etiology of FP may interfere with the dosage and also in the frequency and outcome of treatment. Thus, a faster response was verified in women, young people and people with a paralysis with greater severity. In all comparative studies, there was a need for more than one session of toxin use, and at each new session the use was increased until the maximum level of application of the toxin per patient was reached, thus reaching a stationary or better response phase. Generally the time between sections varied between 6 weeks, 3 months and 4 months[40].

All studies that followed a previous treatment protocol associated the application of BT both on the paralyzed side to reduce spasms and increase strength, and on the non-paralyzed side with reduced muscle hyperactivity and reduced asymmetry. That the relationship between the amount used on each side was counted with a dose 2 times higher on the non-paralyzed side, thus observing the moment of force of the face of the immobilized side immediately after the injection into the contralateral side, which reduces the strength of the non-paralyzed side and draws attention to the Force Redistribution Phenomenon (FRP)[1,33].

Mandrini[42], associated facial muscle training with a mirror or electromyography myofeedback as a complement to BT treatment. The orientation was given to the patients, being asked to perform 3 facial expressions (frown, smile and growl) and be done in front of a mirror, the exercises helped in the creation of a motor memory in the patients, resulting in more coordinated and symmetrical movements, the association proved satisfactory in the treatment of patients.

How efficient the application of BT for the treatment of FP is efficient, it is supported both from patients and from professionals who assist in an installed condition that produces numerous problems to the patient, so the importance of developing more studies and more research so that they can make such treatments increasingly effective, thus helping, patients who, in addition to living with a disease that is difficult to treat, are also submitted to social and emotional problems[1].

3.5 Advantages and Disadvantages

Prior evaluation of patients with an appropriate tool is essential for further evaluation of treatment evolution and response. Although it seems that all professionals dedicated to the treatment of PFP patients support with this aspect, until then it has not been possible an evaluation system that meets all requirements to be widely used, mainly for its simplicity.

In most of the studies evaluated, there was high evidence of success, related to the reduction of symptoms, as well as patient satisfaction, which makes surgical treatment a less advantageous method for patients, due to the aesthetic sequelae that may occur. As a benefit it also finds that the high rates of patient satisfaction in relation to BT use are considered an effective and safe procedure, with fewer contraindications and may be reversible[43].

There is also proof after the sessions, the patients presented Harmony on the face, this partially returning the originals, which made the patients feel happy, confident, returning to their social life, which in most cases is suspended[44].

In the case of type A BT, it was noticed that it effectively fulfills its role when used in the treatment of PFP, providing punctually what was proposed at the beginning of treatment, in most cases returning the symmetry of the face and the naturalness of the traits[45].

Regarding the amounts to be administered, there was a constant variation in the dosage according to the protocol established for each patient, being influenced by etiological factors, gender, age and others. Finally, all the studies used in this study show that the benefits are much higher than the disadvantages of using BT as a therapeutic option in the treatment of FP[35].

Among the disadvantages found regarding the use of Botox, is the fact that it is a temporary method that has a maximum duration of up to 6 months, according to the questions evaluated in the studies presenting a need for reapplication so that it can continue to perform its function, which makes the other methods enter into a constant evolution. Therefore, it is indicated that treatment with BT is added to other treatments, involving physiotherapeutic treatments, which may lead to longer results[43].

Another disadvantage presented is the difficulty of documenting changes in symmetry at rest after BT infiltration. Because there is no range, as there is no complete improvement, the score of this item on the scale does not change. This is because the authors considered that symmetry at rest depends more on the volume of facial reinnervation and is less influenced by rehabilitative treatment, than voluntary movement or syncinesia, and that there should be a significant increase in strength or viable motor units to see changes in scores. That is, they did not take into account that there could be modifications not due to an increase in reinnervation, possibly not yet sufficiently known the time of conception and development of treatment[45].

4. CONCLUSION

BT is a very useful adjuvant in the management of patients with FP sequelae. Its use has increased in recent years, due to its ease of application and the good results observed in selected cases, mainly for correction of mild asymmetries both in the upper third, and in the middle and lower third, in other circumstances, are used for the management of synapses, depending on their degree and severity, either as monotherapy or in combination with other therapies or surgical procedures. Although it is not the only treatment in severe or moderate cases, BT is used as an adjuvant with excellent aesthetic and functional results.

Conflict of Interest

The authors declare no conflict of interest.

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