Review article

Botulinum toxin: a review of its applicability in diseases within the reach of dermatologists

Toxina botulínica: revisão de sua aplicabilidade em doenças ao alcance do dermatologista

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ABSTRACT

In dermatology, botulinum toxin stands out in the treatment of wrinkles and expression lines, mainly being used for aesthetic purposes. However, in recent years the use of botulinum toxin in the treatment of dermatological diseases has grown and shown good results. The present review is aimed at reporting the use of botulinum toxin in clinical conditions that may be treated by dermatologists, exploring its mechanism of action and long-term results, thus gathering practical information for specialist physicians.

Keywords: botulinum toxins; disease; dermatology; skin.

RESUMO

Em dermatologia, a toxina botulínica se destacou no tratamento de rugas e linhas de expressão, sendo utilizada principalmente com finalidade estética. Nos últimos anos, porém, o uso da toxina botulínica no tratamento de doenças dermatológicas tem crescido e apresentado ótimos resultados. O objetivo desta revisão é relatar o uso da toxina botulínica em doenças clínicas que possam ser tratadas pelos dermatologistas, explorando seu mecanismo de ação e resultados a longo prazo, reunindo, assim, informações práticas ao especialista.

Palavras-chave: *toxinas botulínicas; doença; dermatologia; pele.*

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INTRODUCTION

Botulinum toxin is a neurotoxin produced by the anaerobic bacterium called *Clostridium botulinum*.[1] This toxin causes botulism, a severe disease characterized by paralysis of facial muscles, limbs, and paralysis of the respiratory muscles in more aggressive cases, leading to death. The toxin's mechanism of action inhibits the release of acetylcholine in the presynaptic neuromuscular junction, causing flaccid paralysis.[2]

According to Paracelsus (1493-1541), the difference between medicine and poison lies only in the dose. Thus, despite botulinum toxin being considered one of nature's most toxic substances, its therapeutic potential has been explored over the years.[3] The initial application of botulinum toxin in medicine

was performed by Scott in 1970, with an aim at treating strabismus. [4] Since then it has been used for the treatment of neurological and ophthalmic diseases, as well as for cosmetic purposes. [3]

Botulinum toxin can be differentiated into eight serotypes called A, B, Cb, C2, D, E, F, and G. The type A and type B toxins are commercially available. [1] In dermatology, botulinum toxin type A has been widely used for the treatment of wrinkles and expression lines since its approval by the FDA in 2002.

In this manner, the main dermatological use of botulinum toxin is related to the aesthetics of the facial muscles. In recent years, however, botulinum toxin has been used for dermatologic conditions with great therapeutic results. The objective of the present review is to report the use of botulinum toxin in clinical diseases that can be treated by a dermatologist:

Hailey-Hailey disease

Hailey-Hailey disease – also known as benign familial chronic pemphigus – is an uncommon acantholytic dominant autosomal disorder characterized by flaccid blisters and erosions in the intertriginous regions, especially in the axillary and inguinal areas. Erosions associated with local factors such as heat, moisture, microbial colonization, and secondary infections induce the appearance of typical lesions in intertriginous areas. The treatment of Hailey-Hailey disease is traditionally carried out with corticosteroids, and topical and systemic antibiotics, with the use of topical corticosteroids being associated with the development of atrophy and striae, while the antibiotics can lead to bacterial resistance. [1,5]

Lapiere et al. reported the case of a 54-year-old patient diagnosed with Hailey-Hailey disease, who despite topical treatment with corticosteroids, and oral and topical treatment with antibiotics, had not had remission of the condition for three years. The patient underwent an injection of 25U of botulinum toxin A, administered at 20 points on the left axilla, with a 50% reduction in the affected surfaces after three weeks, while the right axilla remained unchanged. Six months after the first injection, the patient was treated with 50U of toxin in each axilla, experiencing complete remission of the disease in both armpits after three weeks. The other regions affected by the disease did not improve or worsen, indicating that there was no spontaneous remission of the disease, and the remission was due to the toxin. [6]

Bessa et al. described the use of botulinum toxin in two sisters, both bearers of Hailey-Hailey disease, who had experienced limited response to the classical treatment. The patients received 125U application of botulinum toxin A: one of them in the axilla and the other in the inguinal region (50 injection points at a distance 1cm from each other, with 2.5U toxin each). One month later, the patient that had the treated axillae showed complete remission of the lesions, and the patient treated in the inguinal region had mild residual erythema and minimal maceration. [7]

The authors linked the improvement in the condition to the decreased local sweating caused by botulinum toxin through the inhibition of acetylcholine in the sympathetic fibers of the sweat glands. The reduction of sweating probably leads to less local irritation (caused by friction) and reduced colonization by microorganisms involved in the exacerbation. Thus, they conclude that botulinum toxin A is a safe and easy to apply treatment option in Hailey-Hailey disease. [6,7]

Raynaud's phenomenon

Raynaud's phenomenon is a condition caused by the spasm of the digital arteries causing pain, numbness, ulceration, and even gangrene in some cases. Botulinum toxin has been shown to produce improvement in Raynaud's phenomenon in several recent studies, in addition to leading to improved digital perfusion that can be visualized on Doppler.

The use of botulinum toxin was first described in 2004 by Sycha et al., who observed improved pain and digital perfusion in two patients, both bearers of Raynaud's phenomenon who underwent treatment with 10U doses of botulinum toxin. [8] In 2009, in a more encompassing study of 19 patients who underwent palmar injection of 50U or 100U of botulinum toxin, it was possible to observe an improvement in pain immediately after the injection, with 84% of patients. Improvement of digital perfusion on Doppler was also observed, with all digital ulcers healing within 60 days. [9]

In a review study on the use of botulinum toxin in Raynaud's phenomenon, Iorio et al. concluded that botulinum toxin acts on vascular smooth muscles by blocking the transmission of norepinephrine and preventing vasoconstriction, as well blocking the alpha-adrenergic receptors[2] leading to the reduction of cold-induced vasoconstriction and pain. In that review, the authors report that different studies disagree regarding the dose, concentration, and distribution of injections, in addition to including Raynaud's phenomena of different etiologies, leaving the impression that a better standardization of the treatment is required. [10]

Notalgia paresthetica

Notalgia paresthetica is a chronic sensory neuropathy that affects the interscapular area, mainly T2-T6, and is characterized by local pruritus and for being a brownish area. Other symptoms are pain, paresthesia, hypoesthesia, hyperesthesia, and a burning sensation. [11] The usual treatments for this condition include local anesthesia, topical corticosteroids, and capsaicin – which do not have good results or long-term effectiveness. [12]

In 2007, Weinfeld proposed that botulinum toxin A would be an effective and safe treatment for notalgia paresthetica. The author conducted intradermal injections of 4U of botulinum toxin A in the affected area, with a distance of 2 cm between points, in two patients with notalgia paresthetica. Followed up with for 18 months, the patients showed significant long-term improvement in the pruritus, associated symptoms, and local hyperpigmentation. [12] It is known that botulinum toxin inhibits the presynaptic release of acetylcholine, and that the acetylcholine mediates the pruritus in atopic dermatitis. Furthermore, the toxin also inhibits Substance P and glutamate – both probably involved in the pruritus – and is capable of

reducing histamine release induced pruritus, thus making it a therapeutic option for pruritic conditions. [13] Wallengren and Bartosik also reported improvement of pruritus in four patients with notalgia paresthetica treated with botulinum toxin. [14]

On the other hand, when treating five patients with notalgia paresthetica, Pérez et al. observed that the improvement of pruritus varies by case, however none of the patients had resolution of the picture or improvement of the brownish stain.[11] Maari et al. also did not find improvement of pruritus or hyperpigmentation in notalgia paresthetica when comparing treatments with botulinum toxin A (10 patients) and placebo (10 patients). Therefore, botulinum toxin's benefits for this disease are still controversial. [15]

Postherpetic neuralgia

Postherpetic neuralgia is a complication of the infection caused by the *Varicella zoster* virus that causes pain and significant discomfort at the site, after the infection has been resolved. The neuralgia – complex mechanism for pain, often very severe –can be explained by an increase in the amount of nerve fibers P in the infection's site and a reduction in the number of wide nerve fibers, which are responsible for inhibiting the transmission of pain. Botulinum toxin exerts an analgesic role in neuralgia by inhibiting substances, such as glutamate, substance P, and the calcitonin-related peptide gene, all involved in the nociception. [16]

Emad et al. evaluated the effectiveness of botulinum toxin in 15 patients with neuralgia postherpetica through 15U injections per 10cm² of affected area, with an improvement of the pain in all patients – although the analgesic effect has decreased over the weeks. [16] Xiao et al. compared the use of botulinum toxin A to a placebo and obtained significant improvements in pain and sleep in patients treated with toxin. [17] In another study with 30 patients, the effectiveness of botulinum toxin was also proven in post-herpetic neuralgia, including tolerability and safety, when compared to a placebo. [18]

The application should be performed at points (with a distance of 1 cm from each other) within the area delimited by the patient, in amounts of 0.5U to 1U per point.

Rosacea

Rosacea is a chronic skin condition characterized by facial erythema, telangiectasia, papules, and inflammatory pustules, with periods of exacerbation and remission, affecting patients' quality of life. The main treatment currently includes topical medicaments such as metronidazole and azelaic acid, oral antibiotic therapy, and laser treatment with variable results.

Dayan et al. carried out a study with 13 patients, all bearers of rosacea, applying intradermal injection of botulinum toxin A totaling 8U to 12U per cheek. The outcome included a reduction of flushing, erythema, and inflammation within one week, persisting for up to three months, without side effects. The authors suggested that the mechanism of action involved is related to a neurogenic component associated to a vascular dysfunction, inflammation, and sebaceous activity. [19]

As described, botulinum toxin can be an innovative option in the treatment of rosacea. Because it is a difficult to control chronic condition that requires ongoing treatment due to periods of constant exacerbation, the toxin can represent a more durable treatment for this disease.

Lichen simplex chronicus

Lichen simplex chronicus, also known as neurodermatitis, is characterized by chronic pruritus that leads to areas of lichenification on the skin, resulting from excessive scratching. It is believed that this pathology is associated with psychological disorders, such as depression and anxiety.

Heckman et al. carried out a pilot study in five lichen simplex chronicus lesions in three patients who underwent intradermal injection of botulinum toxin A. The pruritus decreased within 3 to 7 days in all patients, and lesions completely disappeared between the 2nd and the 4th weeks after treatment, without recurrence during the four months of follow-up. The authors suggested that acetylcholine had mediating action in the pruritus, since it was blocked by the toxin. [20]

Pruritus is conveyed by nerve C fibers, which are sensitive to neurotransmitters, histamine, and other inflammatory mediators such as the substance P and calcitonin gene-related peptide. [21] In a recent study it was demonstrated that botulinum toxin is responsible for reducing histamine-induced pruritus, as well as vasomotor reactions and neurogenic inflammation. Other studies have demonstrated that botulinum toxin A reduces the release of glutamate, substance P, and calcitonin gene-related peptide. [22, 23]

Based on this evidence, botulinum toxin becomes an effective option in the treatment of lichen simplex chronicus, since pruritus is the hallmark of the disease. Furthermore, it emerges as an option for various diseases associated with chronic pruritus.

Parry-Romberg syndrome

Parry-Romberg syndrome is a rare condition characterized by sclerosis and hemifacial lipodystrophy – a form of localized scleroderma. It can be associated with a loss of local hair, retinal vasculopathy, and even headache in the affected side (secondary to trigeminal neuralgia).

Gary et al. described the case of a patient diagnosed with Parry-Romberg syndrome affecting the right-hand side of the forehead, eyebrow, and scalp, with loss of local hair and debilitating pain. At 53 years of age, the patient received 50U of botulinum toxin, distributed in six areas of local involvement, with significant improvement in the pain. Ten years later, the patient had severe facial atrophy, affecting the eyelid, orbit, and masticatory muscles, in addition to evidence of cerebral atrophy associated with low blood flow in the affected side, as visualized by MRI. The patient then underwent injections of botulinum toxin again, with relief of pain, decreased hair loss, and improved memory. [24]

It is believed that the pain relief achieved after intradermal botulinum toxin is caused by an increase in local perfusion, as botulinum toxin causes vasodilation by causing relaxation of

smooth muscles. Thus, if tissular perfusion can increase with repeated applications of botulinum toxin, it is possible that atrophies caused by vascular disease may have a new option of treatment with the use of botulinum toxin.

Erythromelalgia

Erythromelalgia is a neuropathy characterized by severe pain, heat, and erythema in the affected areas, and is known to be difficult to treat. The pain caused by the burning sensation worsens with heat and is relieved with cold. Lin et al. treated one patient with significant symptoms of the disease who had been refractory to multiple prior treatments (propranolol, escitalopram, alprazolam, gabapentin, aspirin, prednisone, amitriptyline, venlafaxine, duloxetine, or even combinations of these drugs) with botulinum toxin injections. A12.5U amount was injected subcutaneously on each cheek with an improvement of pain and redness within one week. The authors hypothesized that the pain present in erythromelalgia is neuropathic and that the erythema and heat are induced by an intense neurogenic inflammation. Having botulinum toxin A proven effective in neuropathic pain and also in diabetic neuropathy, it leads to good outcomes in erythromelalgia. The improvement in the erythema and redness can be explained by the inhibition of proinflammatory neurotransmitters, such as calcitonin gene-related peptide, the substance P and glutamate. [25]

Eccrine Angiomatous Hamartoma (EAH)

Eccrine Angiomatous Hamartoma (EAH) is a benign tumor composed of capillary channels and eccrine glands, that usually appears in childhood, in the distal part of the limbs, arising as a nodule or plaque, with red, blue, violet, brown, yellow, or skin colored pigment. It can be painful, hyperhidrotic, or cause excessive sweating. When associated with pain or hyperhidrosis, it can be treated with surgical excision or laser therapy.

Barco et al. reported a case of a 12-year-old patient with an EAH measuring roughly 6cm in the sacral region, with complaint of intense sweating in the region. Doses of 2.5U botulinum toxin A were injected at 14 points (distant 1.5cm from each other) in the region, resulting in an absence of sweating for five months. Through the blocking of acetylcholine, botulinum toxin reduces the activity of smooth striated muscles and of autonomic structures, reducing the secretion of eccrine glands – and is therefore widely used in hyperhidrosis. [26]

Based on this case report, it is possible to conclude that botulinum toxin A arises as a therapeutic option for symptomatic EAH, improving the quality of life in patients who prefer to avoid the surgical treatment of this pathology.

Multiple eccrine hidrocystomas

Eccrine hidrocystoma is a benign and asymptomatic tumor of the sweat glands that originates from the cystic dilatation of the gland's excretory duct. It is located in the centrofacial area, and is characterized by 2-6mm skin-colored, vesiculopapular lesions, usually multiple in number. [27,28] Although a single eccrine hidrocystoma can be easily treated with excision, surgical elimination of multiple lesions can be problematic depending on their amount and location.[29] Blugerman, Schavelzon and D'Angelo initially described the benefits of botulinum toxin A application in multiple eccrine hidrocystomas, highlighting the ease of application and lack of local scar. [29]

Correia et al. described two cases of multiple eccrine hidrocystomas treated with botulinum toxin A. The first patient had multiple hidrocystomas in the nose and nasolabial region that had been refractory to various treatments including CO_2 laser, cryosurgery, and oral isotretinoin. She underwent intradermal injections of botulinum toxin A totaling 50U (1 to 3U perilesionally, with a distance of 5mm). The patient had complete clinical resolution in five days, and there was no evidence of lesions for six months. Nevertheless recurrence was observed eight months after. The second patient had lesions distributed in the frontal and periorbital regions, and having undergone perilesional injections of botulinum toxin A (1U to 4U) presented a dramatic response in five days, and remained in complete clinical resolution for 11 months.[28] Woolery and Raipara also reported good results with the use of botulinum toxin A in eccrine hidrocystomas. [30]

Kontochristopoulos et al. recorded the treatment of a patient with multiple eccrine hidrocystomas in the centrofacial region who had been unresponsive to various previous treatments. She underwent 1U perilesional injections of botulinum toxin in the superficial dermis with a distance of 40mm between applications, totaling 60U. Improvement was observed in seven days, with complete resolution in 14 days, without recurrence for four months. As a side effect, the patient experienced difficulty with smiling in just the two days after the treatment, due to a compromise of perioral muscles, besides improvement in rhytids located near the lesions. [28]

The probable mechanism of action for botulinum toxin is involved in the treatment of eccrine hidrocystoma, consisting of the reduction of sweating due to the chemical blocking that takes place in the sweat glands. [29] Thus, botulinum toxin A emerges as a new treatment option for patients with multiple hidrocystomas resistant to other treatments, with the advantage of being simple, well-tolerated, producing excellent results and having no risk of scarring.

Inverse psoriasis

Inverse psoriasis is a form of psoriasis that affects flexural areas and is usually associated with chronic intertrigo, and is characterized by erythematous plaques with different degrees of infiltration, pruritus, and local burning sensation. The treatment of this disease can be difficult and requires a different approach as compared to that used to treat its common form, due to the skin's sensitivity in the affected areas.[31]

Botulinum toxin A can be a treatment option for inverse psoriasis due to its action of reducing both local sweat in the neuroglandular junction (and consequently, decreasing the maceration and infection), and inhibiting neuropeptides and other substances responsible for inflammation and pain transmission.[32]

Zanchi et al. demonstrated the first positive results with the use of botulinum toxin A in inverse psoriasis. They have carried out a study where 15 patients with inverse psoriasis were treated with 2.4U injections of botulinum toxin A (2.8cm between points), totaling 50U or 100U of toxin per patient, according to the lesion's size. There was improvement of the extent of the erythema and the intensity of infiltration in 87% of patients, an outcome that continued for 12 weeks after the treatment, which was well tolerated by patients, with an absence of side effects.[31] Saber, Brassard, and Brnohanian reported the case of a patient with inverse psoriasis and axillary hyperhidrosis, with significant improvement of the picture after one week of treatment with botulinum toxin A.[33]

Acting on the control of inflammation and of substances involved in the mechanism of inverse psoriasis, botulinum toxin can be considered a new treatment option.

Hyperhidrosis

Primary or idiopathic hyperhidrosis is a benign condition of unknown etiology characterized by excessive sweating in specific body sites, usually the palms, soles, axillae and, occasionally, the face and scalp. It is a common condition, affecting up to 3% of the global population and can even trigger psychological, social, and occupational problems. Until recently, treatment options were ineffective (e.g. aluminum salts or glutaraldehyde), complicated (e.g. iontophoresis) or extremely invasive (e.g. excision of axillary sweat glands). Other approaches have included the use of systemic drugs (sometimes with side effects), psychotherapy, and thoracic sympathectomy.

In 2004, the use of botulinum toxin was approved by the FDA for treatment of difficult to control axillary hyperhidrosis.[34] In the technique described by Del Boz et al., it is recommended that the axillary area to be treated be identified through a starch-iodine test. After defining the quadrants, antiseptic is applied, and topical or injectable anesthetic can be applied in order to minimize the discomfort. A 50U dose of toxin is applied in each axilla, intradermally in 0.1vml injections, observing a distance of 2cm between the points. Clinical improvement usually develops within one week after application, which can be repeated once a drop-off in clinical effect occurs.[35]

The effectiveness of botulinum toxin injections in axillary hyperhidrosis ranges from 2 to 24 months. Lecouflet et al. reported that the duration of the injection's effect increases with repeat treatments, allowing patients to reduce the frequency of injections over time. This can be explained by the action of botulinum toxin, which blocks synapses in the motor neurons, causing degeneration of the terminal axon, which in turn grows again, lending a transitory character to the effect of botulinum toxin. Due to the repeated injections of toxin, however, the terminal axon regeneration becomes slower, allowing a longer-lasting effect.[36]

Although the only approved indication for the treatment of hyperhidrosis with botulinum toxin is the persistent, severe primary axillary hyperhidrosis that is resistant to topical treatment, more recently other body sites have been successfully treated for hyperhidrosis with botulinum toxin.[35]

Facial hyperhidrosis can be safely and effectively treated with botulinum toxin, nevertheless in order to avoid side effects on facial muscles, very small amounts should be injected (0.3U), at distances of 1- 2cm. [37] In palmar hyperhidrosis, the result of the application of 100U of toxin on each palm lasts about 6 months, remarkably improving patients' quality of life. Injections in the palms of the hands can lead to transient weakness of the small muscles of the hands due to the diffusion of the toxin.[38] The treatment for plantar hyperhidrosis has also proven effective, with 100U in each sole remaining effective for 3 months. [39]

The anhidrotic effect of botulinum toxin can be noticed within 2-4 days after the application. Several studies have demonstrated its efficacy in 90% of patients. Despite the fact that the apocrine glands are innervated by adrenergic fibers, treatment with botulinum toxin also improves the unpleasant odor of sweat, with a mechanism that reduces sweating and therefore the environment conducive to bacterial growth. [38]

Botulinum toxin for treating focal hyperhidrosis has proven to be a very effective and safe option, which improves patients' quality of life – especially when other treatments are ineffective. [38]

Masseter muscle hypertrophy

Benign hypertrophy of the masseter muscle is an unusual clinical phenomenon of unknown etiology, characterized by swelling in the mandible's angle. It is occasionally associated with facial pain and can be important enough to compromise the aesthetics of the face. Several treatment options for hypertrophy of the masseter muscle have been reported, ranging from simple drug therapy to invasive surgical reduction. The application of botulinum toxin type A in the masseter muscle is considered a less invasive modality, able to sculpt the angles of the face. [40, 41]

The use of botulinum toxin for the treatment of the hypertrophic masseter muscle was initially described by Moore and Wood.[42] Kim, Park, and Park have evaluated 121 patients who received injections of 100 - 140U of botulinum toxin into the masseter, with a decrease in the muscle's thickness then observed through ultrasonography.[43] Aydilet al. conducted a retrospective study analyzing 28 patients with masseter hypertrophy, who underwent six toxin botulinum treatment courses in six-month intervals, concluding that the toxin was capable of reducing the thickness of the masseter muscle.[44]

In a review study on the efficacy and safety of botulinum toxin type A for the treatment of the masseter hypertrophy, Fedorowicz et al. did not identify any randomized controlled scientific study that confirmed the efficacy of botulinum toxin when injected in that muscle, for people bearing benign hypertrophy of the masseter. [40]

However, several studies have demonstrated that botulinum toxin A is a safe and effective treatment for masseter muscle hypertrophy, with significant long-term results and a positive correlation between the number of applications and the reduction of muscle volume. Its use has in some cases also been cor-

related with the decrease of associated pain. [45]

Dyshidrosis

Dyshidrosis – or dyshidrotic eczema – is characterized by the occurrence of vesicular lesions, usually in the palmar and/or plantar region, of a chronic and recurrent nature. Multiple etiopathogenetic factors are reported, including emotional factors, atopy, medications, and contact with substances.

Botulinum toxin has recently been used in the treatment of focal hyperhidrosis, which is often associated with dyshidrosis, for it acts as an aggravating factor in almost 40% of patients with dyshidrotic hand eczema. According to Swartling et al., botulinum toxin A is a valuable alternative for patients who are refractory to treatment of dyshidrotic eczema – especially those with associated hyperhidrosis or that which worsens during summer. It acts as a potent inhibitor of the release of acetylcholine, which induces the production and release of sweat. The halting of sweating leads to an improvement in outcomes and a reduction in the number of recurrences. [46] In addition to halting sweat production, there are reports of a possible antipruritic effect, suggesting that it not only interacts with the release of acetylcholine, but also with the substance P. [47]

In a prospective pilot study, Wollina et al. compared left and right hands in order to investigate whether the denervation of the sweat gland by botulinum toxin would be superior to a standard, topical corticosteroids-based therapy. The improvement of dyshidrosis was more significant with toxin than under topical therapy. Pruritus and the vesiculation were inhibited early when corticosteroids and botulinum toxin were used in combination. [47]

Botulinum toxin acts both on the reduction of perspiration – which aggravates dyshidrosis – and on the inhibition of the sensory system – with a direct effect on the ascending fibers through the inhibition of neurotransmitters – making it a therapeutic option in the treatment of dyshidrosis.

Hypertrophic scars

Hypertrophic scars occur due to excessive deposition of fibrosis and extracellular matrix, with unpleasant aesthetic and functional impacts. The etiology of their development has not been clearly determined; therefore its clinical management remains a problem. Many treatments are available, including surgical excision, injection of corticosteroids, radiation therapy, laser pressure, and therapy –though they do not always bring about good therapeutic results.

Recent studies have reported that botulinum toxin type A can inhibit the growth of hypertrophic scars and improve their appearance. Wang et al. created a model of hypertrophic scarring in the ears of rabbits, through which they discovered that botulinum toxin type A can inhibit the formation of scars and fibroblast activity. This can significantly reduce the expression and the proportion of collagen I and III in the hypertrophic scar.[48] Furthermore, there is evidence that botulinum toxin is involved in cell cycle regulation, reducing the TGF-α1 growth factor, which is expressed in the fibroblasts of hypertrophic scars.

An intralesional injection of botulinum toxin was performed in a recent study at doses of 70 - 140U per session, with the application being repeated every three months, for up to nine months. During the course of one year, 3 of the 12 patients had excellent results, 5 achieved good results, and 4 had reasonable results. The analysis of the lesions showed a reduction in their periphery in addition to flattening in all patients. There were no recurrences in the 1-year follow-up after the treatment.[49]

Notwithstanding, in another recent study the authors performed intralesional injections of 70 - 140U of botulinum toxin in keloids in four patients every two months, for six months, with an absence of clinical improvement. The assessment of the lesion's volume performed with 3D optical profilometry did not evidence changes after the treatment.[50]

In a recent review study on the treatment of keloids, Gauglitzet al. concluded that despite the fact that the reduction in tension strength caused by the intradermal injection of botulinum toxin corresponds to the ideal mechanism of action for the aesthetic treatment of scars, botulinum toxin's clinical efficacy in those lesions remains uncertain, requiring more in-depth comparative studies aimed at proving its action in scarring.[51]

Non-dermatological diseases having a therapeutic approach within the reach of dermatologists

Below are reported non-dermatological conditions that can nevertheless be successfully treated by a dermatologist, taking into consideration the comprehensive use of botulinum toxin by this expert and his or her experience with the toxin:

MIGRAINE

Migraine corresponds to the sensation of pain due to the activation of the afferent trigeminal that innervates the vasculature of the meninges and runs towards the trigeminal caudate nucleus. The pain is described in extracranial regions innervated by somatic afferent fibers that protrude in the homologous regions in the trigeminal caudate nucleus. This viscerosomatic conversion leads to the onset of pain in the meningeal afferent fibers to the extracranial dermatomes. The use of botulinum toxin in these dermatomes has been showing effectiveness in the treatment of chronic migraine headaches.

In 2010, the use of botulinum toxin type A was approved by the FDA (US Food and Drug Administration) for the prevention of chronic migraine, becoming the second choice treatment for adult patients who do not respond to drug therapy. The mechanism involved is the action of botulinum toxin in nociceptive mediators such as glutamate, substance P, and calcitonin gene-related peptide, in controlling the pain.[52]

Several randomized, placebo-controlled studies have shown the us of botulinum toxin for the treatment of chronic migraine. Blumenfeld et al., described a technique in which 155U of botulinum toxin A are distributed in 31 injections of 5U (applying 5U in each corrugator muscle, 5U in the procerus, 10U on each side of the frontalis muscle, 20U in each temporal muscle, 15U on each side of the occipital, 10U in each side of the cervical paraspinal region, and 15U on each side of

the trapezius muscle. One thousand, three hundred and eighty four (1,384) patients with chronic migraine were treated in this study, received at least 155U botulinum toxin each in 7 muscles of the neck and head every 12 weeks for 5 cycles, with an outcome of effectiveness and safety in the prophylaxis of chronic migraine. [52]

Lin et al. evaluated 98 patients with chronic migraine who received 100U of toxin injected in 21 points or 155U injected in 31 points of seven muscles of the head and neck. Around 40% of patients reported a 30% reduction of chronic migraines in the 12 weeks after a single application. [53] In another study, Aurora et al. showed improvement in the treatment of chronic headache with botulinum toxin when compared to a placebo, also demonstrating the need for maintenance treatment and the benefit accumulated over time with continued prophylaxis. [54]

Thus, it is possible to conclude that botulinum toxin can be used in the treatment of chronic migraine with positive results due to its analgesic action, especially in patients with difficulty in accepting the pharmacological treatment or even in those who are refractory to clinical therapy.

Bruxism

Bruxism is a condition characterized by the non-functional contact of the teeth of the mandible with those of the maxilla, generating the gnashing of teeth due to the repetitive and unconscious contraction of the masseter and temporalis muscles, leading to discomfort and damage to the teeth. The causes are poorly defined, however may involve behavioral, genetic, or functional alterations of the central nervous system.

No permanent therapy has proven effective in the treatment of bruxism. Current treatments focus on the management of symptoms and the prevention of complications, with oral appliances, and pharmacological and behavioral treatments the most frequently used methods. Some studies demonstrate positive results obtained with the use of botulinum toxin in the treatment of bruxism, what can be attributed to the decrease in the intensity of the contraction of the jaw occlusion muscles. [55]

Alonso-Navarro et al. treated 19 patients with severe bruxism with botulinum toxin injections in the masseter and temporalis muscles, at doses of 25 - 40U per muscle. These patients were followed up with for periods ranging from 6 months to 11 years. The result suggested success in the treatment of bruxism, with the effect's duration ranging from 13 to 26 weeks.

In a review study on the effectiveness of botulinum toxin in bruxism, Long et al. concluded that botulinum toxin injections could reduce the frequency of bruxism events, decrease the level of pain induced by this disease and meet the needs of the patients treated. When compared with oral appliances, botulinum toxin is equally effective. [56] In light of this, botulinum toxin arises as a safe, easy to use therapeutic option with great results in bruxism.

Depression

Depression affects about 121 million people worldwide, and is often a disabling disease. Although there are several treatments available, in many cases the therapeutic response is not satisfactory, with the condition becoming chronic in a number of patients. New therapeutic techniques are required to improve the prognosis of depressive disorders. [57] Finzie and Wasserman first described the use of botulinum toxin for the treatment of depression: 9 out of 10 patients treated with toxin did not present a depression picture after two months of treatment, with all patients showing improvement in mood. [58]

Negative emotions such as anger, fear, and sadness, which prevail in depression, are associated with the activation of the corrugator and procerus muscles in the glabellar region of the face. The treatment of the glabellar region with botulinum toxin produces a relative change in facial expressions of nervousness, sadness, and fear into a happiness expression, and can have an emotional impact. Patients who underwent this treatment reported improved emotional well being, in addition to an aesthetic benefit. The treatment is responsible for attenuating the activation of the limbic region of the brain, which was caused during voluntary contraction of the corrugator and procerus, thereby indicating that the feedback from facial muscles can modulate the processing of emotions. [57]

In a randomized, controlled study, 15 patients with depressive disorder underwent botulinum toxin injections in the glabellar region, while another 15 underwent injections of 9% NaCL0, as a placebo. The female patients received a total of 29U (7U in the procerus muscle, 6U in the medial region of the corrugators, and 5U in the lateral region of the corrugators). The male patients received an additional 2U in each of the sites (totaling 39U) due to their more abundant muscle mass. It was possible to observe an improvement of 47.1% in the symptoms of depression in the control group and 9.1% in the placebo group, at six weeks after the treatment. The authors state that a single treatment in the glabellar region with botulinum toxin is associated with the relief of depression, and that the facial muscles not only express, but also regulate emotional states. [57]

In a randomized, double-blind, placebo-controlled study, Magid et al. followed up with patients with depressive disorder who underwent injections of botulinum toxin (29U in women and 39U in men) and of placebo, concluding that there was a significant improvement in symptoms of depression in patients treated with botulinum toxin as compared to the placebo. [59] More recently, Wollmer et al. also demonstrated in a randomized controlled trial that botulinum toxin injections in the glabellar region produce improvements in the symptoms of depression, stating that although the mechanism of action is unknown, hypotheses associated with the feedback caused by the facial muscles should be considered. [60]

Furthermore, it is known that substance P levels are intimately involved in the pathogenesis of depression. Recent studies have reported the antidepressant effect of substance P's antagonist's receptor. Guiard et al. concluded that high levels of substance P in the brain have an important role in the pathophysiology of depression. [61] The transmission of substance P is also stimulated in stress and anxiety situations. Just as botulinum toxin is responsible for inhibiting the neurotransmission of substance P, the success in treating depression with botulinum toxin

can also be explained by this mechanism of action.

In this manner, it is possible to conclude that botulinum toxin injections can be applied to the glabellar region by dermatologists not only for aesthetic treatment, but also as a therapy in depressed patients, especially when they do not respond to pharmacological treatments.

CONCLUSION

The present study explored the many uses of botulinum toxin in dermatology, which go beyond aesthetics. The authors included various dermatological diseases that find in botulinum toxin an effective and differentiated therapeutic option, exploring its mechanism of action and results in the long run. Through extensive literature review, it was possible to gather information that is crucial to the conscientious dermatologist in his or her permanent search for new treatment options for his or her patients.

REFERENCES

1. Shilpa PS, Kaul R, Sultana N, Bhat S. Botulinum toxin: The Midas touch. J Nat Sci Biol Med. 2014;5(1):8-14.
2. Arnon SS, Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, et al. Botulinum toxin as a biological weapon: medical and public healthmanagement. JAMA. 2001;285(8):1059-70.
3. Mahajam ST, Brubaker, L. Botulinum toxin: from life-threatening disease to novel medical therapy. Am J Obstet Gynecol. 2007;196(1):7-15.
4. Scott, AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. Invest Ophthalmol. 1973;12(12):924-7.
5. Rossolini GM, Mantegoli E. Antimicrobial resistence in Europe and its potential impacto n empirical therapy. Clin Microbiol Infect. 2008;14(Suppl 6):2-8.
6. Lapiere JC, Hirsh A, Gordon KB, Cook B, Montalvo A. Botulinum toxin type A for the treatment of axillary Hailey-Hailey disease. Dermatol Surg. 2000;26(4):371-4.
7. Bess GR, Manzoni AN, Bonamigo RR, Grazziotin TC, Weber MB. Tratamento da doença de Hailey-Hailey com toxina botulínica tipo A. An Bras Dermatol. 2010; 84 (5): 717-22.
8. Sycha T, Graninger M, Auff E, Schnider P. Botulinum toxin in the treatment of Raynaud's phenomenon: a pilot study. Eur J Clin Invest. 2004;34(4):312-3.
9. Neumeister MW, Chambers CB, Herron MS, Webb K, Wietfeldt J, Gillespie JN, et al. Botox therapy for ischemic digits. Plast Reconstr Surg 2009;124(1):191-201.
10. Iorio ML, Masden DL, and Higgins JP. Botulinum Toxin A Treatment of Raynaud's Phenomenon: A Review. Seminars in Arthritis and Rheumatism.2012;41(4):599-603.
11. Pérez-Pérez L, García-Gavín J, Allegue F, Caeiro JL, Fabeiro JM, Zulaica A. Notalgia paresthetica: treatment using intradermal botulinum toxin A. Actas Dermosifiliogr. 2014;105(1):74-7.
12. Weinfeld PK. Successful treatment of notalgia paresthetica with botulinum toxin type A. Arch Dermatol. 2007;143(8):980-2.
13. Gazerani P, Pedersen NS, Drewes AM, Arendt-Nielsen L. Botulinum toxin type A reduces histamine-induced itch and vasomotor responses in human skin. Br JDermatol. 2009;161(4):737-45.
14. Wallengren J, Bartosik J. Botulinum toxin type A for neuropathic itch. Br J Dermatol. 2010;163(2): 424-6.
15. Maari C, Marchessault P, Bissonnette R. Treatment of notalgia paresthetica with botulinum toxin A: a double-blind randomized controlled trial. J Am Acad Dermatol. 2014;70(6):1139-41.
16. Emad MR, Emad M, Taheri P. The efficacy of intradermal injection of botulinum toxin in patients with post-herpetic neuralgia. Iran Red Crescent Med J. 2011 ;13(5):323-7.
17. Xiao L, Mackey S, Hui H, Xong D, Zhang Q, Zhang D. Subcutaneous injection of botulinum toxin a is beneficial in postherpetic neuralgia. Pain Med. 2010;11(12):1827-33.
18. Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single-dose, placebo-controlled trial. Clin J Pain. 2013;29(10):857-64
19. Dayan SH, Pritzker RN, Arkins JP. A new treatment regimen for rosacea: onabotulinumtoxinA. J Drugs Dermatol. 2012;11(12):e76-9.
20. Heckmann M, Heyer G, Brunner B, Plewig G. Botulinum toxin type A injection in the treatment of lichen simplex: an open pilot study. J Am Acad Dermatol. 2002;46(4):617-9.
21. Wollina U. Botulinum Toxin: Non-cosmetic Indications and Possible Mechanisms of Action. J Cutan Aesthet Surg. 2008;1(1):3-6.
22. McMahon HT1, Foran P, Dolly JO, Verhage M, Wiegant VM, Nicholls DG. Tetanus toxin and botulinum toxins type A and B inhibit glutamate, gamma-aminobutyric acid aspartate and met-enkephalin release from synaptosomes. Clues to the locus of action. J Biol Chem. 1992;267(30):21338-43.
23. Purkiss J, Welch M, Doward S, Foster K. Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms. Biochem Pharmacol. 2000; 59(11):1403-6.

24. Borodic GE, Caruso P, Acquadro M, Chick S. Parry-Romberg syndrome vasculopathy and its treatment with botulinum toxin. Ophthal Plast Reconstr Surg. 2014;30(1):e22-5.
25. Lin KH, Wang SJ, Fuh JL, Chen SP. Effectiveness of botulinum toxin A in treatment of refractory erythromelalgia. J Chin Med Assoc. 2013;76(5):296-8.
26. Barco D, Baselga E, Alegre M, Curell R, Alomar A. Successful treatment of eccrine angiomatous hamartoma with botulinum toxin. Arch Dermatol. 2009;145(3):241-3.
27. Correia O, Duarte AF, Barros AM, Rocha N. Multiple eccrine hidrocystomas-from diagnosis to treatment: the role of dermatoscopy and botulinum toxin. Dermatology. 2009;219(1):77-9.
28. Kontochristopoulos G, Markantoni V, Stefanaki C, Kanelleas A, Rigopoulos D,Gregoriou S. Multiple eccrine hidrocystomas treated with botulinum toxin A. Clin Exp Dermatol. 2011;36(1):95-6.
29. Blugerman G, Schavelzon D, D'Angelo S. Multiple eccrine hidrocystomas: a new therapeutic option with botulinum toxin. Dermatol Surg. 2003;29(5):557-9.
30. Woolery-Lloyd H, Rajpara V, Nijhawan RI. Treatment for multiple periorbital eccrine hidrocystomas: botulinum toxin A. J Drugs Dermatol. 2009;8(1):71-3.
31. Zanchi M, Favot F, Bizzarini M, Piai M, Donini M, Sedona P. Botulinum toxin type-A for the treatment of inverse psoriasis. J Eur Acad Dermatol Venereol. 2008;22(4):431-6.
32. Eedy DJ, Johnston CF, Shaw C, Buchanan KD. Neuropeptides in psoriasis: na immunocytochemical and radioimmunoassay study. J Invest Dermatol 1991;96(4): 434-8.
33. Saber M, Brassard D, Benohanian A. Inverse psoriasis and hyperhidrosis of the axillae responding to botulinum toxin type A. Arch Dermatol. 2011;147(5):629-30.
34. Chen S. Clinical uses of botulinum neurotoxins: current indications,limitations and future developments. Toxins (Basel). 2012;4(10):913-39.
35. Del Boz J, Padilla-España L, Segura-Palacios JM. Botulinum Toxin Injection Technique for Axillary Hyperhidrosis - Actas Dermosifiliogr. 2014;105(5):517-8
36. Lecouflet M, Leux C, Fenot M, Célerier P, Maillard H. Duration of efficacy increases with the repetition of botulinum toxin A injections in primary axillary hyperhidrosis: a study in 83 patients. J Am Acad Dermatol. 2013;69(6):960-4.
37. Komericki P, Ardjomand N. Hyperhidrosis of face and scalp: repeated successful treatment with botulinum toxin type A. Indian J Dermatol Venereol Leprol. 2012;78(2):201-2.
38. Campanati A, Bernardini ML, Gesuita R, Offidani A. Plantar focal idiopathic hyperhidrosis and botulinum toxin: a pilot study. Eur J Dermatol. 2007;17(1):52-4.
39. Läuchli S, Burg G. Treatment of hyperhidrosis with botulinum toxin A. Skin Therapy Lett. 2003;8(7):1-4.
40. Fedorowicz Z, van Zuuren EJ, Schoones J. Botulinum toxin for masseter hypertrophy. Cochrane Database of Syst Rev. 2013;9:CD007510.
41. Almeida AT.Tratamento da hipertrofia do masseter.In: Hexsel, Doris, Almeida, Ada Trindade, editores. Uso cosmético da toxina botulínica. Porto Alegre: Editora AGE: 2002. p. 185-7.
42. Moore AP, Wood GD. The medical management of masseteric hypertrophy with botulinum toxin type A. Br J Oral Maxillofac Surg. 1994;32(1):26-8.
43. Kim NH, Park RH, Park JB. Botulinum toxin type A for the treatment of hypertrophy of the masseter muscle. Plast Reconstr Surg. 2010;125(6):1693-705.
44. Aydil B, Başaran B, Unsaler S, Süoğlu Y. [The use of botulinum toxin type A in masseteric muscle hypertrophy: long-term effects and lasting improvement]. Kulak Burun Bogaz Ihtis Derg. 2012;22(5):249-53.
45. Rijsdijk BA, van ES RJ, Zonneveld FW, Steenks MH, Koole R. Botulinum toxin type A treatment of cosmetically disturbing masseteric hypertrophy. Ned Tijdschr Geneeskd. 1998;142(10):529-32.
46. Swartling C, Naver H, Lindberg M, Anveden I. Treatment of dyshidrotic hand dermatitis with intradermal botulinum toxin. J Am Acad Dermatol. 2002;47(5):667-71.
47. Wollina U, Karamfilov T. Adjuvant botulinum toxin A in dyshidrotic hand eczema: a controlled prospective pilot study with left-right comparison. J Eur Acad Dermatol Venereol. 2002;16(1):40-2.
48. Wang L, Tai NZ, Fan ZH. Effect of botulinum toxin type A injection on hypertrophic scar in rabbit ear model. Zhonghua Zheng Xing Wai Ke Za Zhi. 2009;25(4):284-7.
49. Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. Plast Reconstr Surg. 2009;124(5): 275e-277e.
50. Gauglitz GG, Bureik D, Dombrowski Y, Pavicic T, Ruzicka T, Schauber J. Botulinum toxin A for the treatment of keloids. Skin Pharmacol Physiol. 2012;25(6):313-8.
51. Gauglitz GG. Management of keloids and hypertrophic scars: current and emerging options. Clin Cosmet Investig Dermatol. 2013;6:103-14.
52. Blumenfeld A, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, Binder WJ. Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. Headache. 2010;50(9):1406-18.
53. Lin KH, Chen SP, Fuh JL, Wang YF, Wang SJ. Efficacy, safety, and predictors of response to botulinum toxin type A in refractory chronic migraine: a retrospective study. J Chin Med Assoc. 2014;77(1):10-5.
54. Aurora SK, Dodick DW, Diener HC, DeGryse RE, Turkel CC, Lipton RB, et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta Neurol Scand. 2014;129(1):61-70.
55. Lee SJ, McCall WD Jr, Kim YK, Chung SC, Chung JW. Effect of botulinum toxin injection on nocturnal bruxism: a randomized controlled trial. Am J Phys Med Rehabil. 2010;89(1):16-23.
56. Long H, Liao Z, Wang Y, Liao L, Lai W. Efficacy of botulinum toxins on bruxism: an evidence-based review. Int Dent J. 2012;62(1):1-5
57. Wollmer MA, de Boer C, Kalak N, Beck J, Götz T, Schmidt T, et al. Facing depression with botulinum toxin: a randomized controlled trial. J Psychiatr Res. 2012;46(5):574-81.
58. Finzi E, Wasserman E. Treatment of depression with botulinum toxin A: a case series. Dermatol Surg. 2006;32(5):645-9; discussion 649-50.
59. Magid M, Reichenberg JS, Poth PE, Robertson HT, LaViolette AK, Kruger TH, et al. Treatment of major depressive disorder using botulinum toxin a: a 24-week randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2014;75(8):837-44.
60. Wollmer MA, Kalak N, Jung S, de Boer C, Magid M, Reichenberg JS, et al. Agitation predicts response of depression to botulinum toxin treatment in a randomized controlled trial. Front Psychiatry. 2014;5:36.
61. Guiard BP, Guilloux JP, Reperant C, Hunt SP, Toth M, Gardier AM. Substance P neurokinin 1 receptor activation within the dorsal raphe nucleus controls serotonin release in the mouse frontal cortex. Mol Pharmacol. 2007;72(6):1411-8.