Updates on the cosmiatric and therapeutic use of botulinum toxin

Atualizações do uso cosmiátrico e terapêutico da toxina botulínica

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ABSTRACT

Botulinum toxin has transient flaccid neuromuscular paralysis as its mechanism of action. Recent studies are identifying new ways to use botulinum toxin for a variety of purposes, both in the aesthetic and in the therapeutic field. This work aimed to conduct a literature review on these applications. In the aesthetic field, botulinum toxin has shown benefit in the treatment of hypertrophic scars, rejuvenation of the scrotal region, definition of the gastrocnemius muscle, and microdoses use. In the treatment of pathologies, the review has shown that botulinum toxin may be useful for the treatment of post-herpetic neuralgia and other pain syndromes, craniofacial hyperhidrosis, rosacea, and Hailey-Hailey disease.

Keywords: Botulinum toxins; Botulinum toxins, Type A; Esthetics; Pruritus; Rejuvenation; Cicatrix; Cicatrix, Hypertrophic

RESUMO

A toxina botulínica tem como mecanismo de ação a paralisia neuromuscular flácida transitória. Estudos recentes estão identificando novas formas de uso da toxina botulínica para diversos fins, tanto no campo estético quanto no terapêutico. Este trabalho teve como objetivo realizar uma revisão bibliográfica sobre essas aplicações. No âmbito estético, a toxina botulínica demonstrou benefício em tratamento de cicatrizes hipertróficas, rejuvenescimento da região escrotal, definição do músculo gastrocnêmio e sendo usada em microdoses. Já no tratamento de patologias, a revisão demonstrou que a toxina botulínica pode ser útil para tratamento da neuralgia pós-herpética e de outras síndromes álgicas, da hiperidrose craniofacial, da rosácea e da doença de Hailey-Hailey.

Palavras-Chave: *Toxinas botulínicas tipo A; Estética; Toxinas botulínicas; Prurido; Rejuvenescimento; Cicatriz; Cicatriz hipertrófica*

Review Articles

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INTRODUCTION

Botulinum toxin (BT) is a neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*, which causes botulism, a serious disease characterized by the paralysis of the facial muscles, limbs and even respiratory muscles, which can lead to death. The mechanism of action of botulinum toxin is to determine transient flaccid neuromuscular paralysis through the chemical denervation process. Thus, it binds to the presynaptic receptor in the neuromuscular junction; the complex formed is endocytosed, followed by synaptosomal-associated protein-25 cleavage (SNAP-25), which culminates in the blockade of acetylcholine release, preventing muscle contraction until the function is repaired again in approximately three to six months.[1,2,3]

Botulinum toxin can be differentiated into eight serotypes named A, B, Cb, C2, D, E, F, and G. The types A and B are commercially available. In dermatology, botulinum toxin type A is the most used since the FDA approved it in 2002.[3]

Botulinum toxin was used therapeutically for the first time in the 1960s by ophthalmologists in San Francisco to correct strabismus.[2] Later, new studies were conducted and its use was progressively expanded to other therapeutic areas until, finally, in 1989, it was used for the first time with an aesthetic purpose, initially to correct asymmetries by facial paralysis and later, in 1992, for correction of expression wrinkles.[2]

In esthetics, it has a well-defined use to treat glabellar and periorbital wrinkles. However, more recent research with new application techniques, formulations, and use in combination with fillers and other procedures has revealed its potential for better aesthetic results, new uses, and increased patient satisfaction.[1]

With non-aesthetic goals, botulinum toxin has been used to treat inflammatory skin diseases such as acne, rosacea, psoriasis, diseases caused or exacerbated by hyperhidrosis, and to improve the appearance of post-surgical scars.[1]

The objective of this review is to report the new uses of botulinum toxin both in aesthetics and in the therapeutic field.

Aesthetic uses

Botulinum toxin is an established option to minimize signs of aging and tired facial appearance. Its use is mainly related to the musculature of the facial mime. However, new cosmetic applications have shown excellent results and should be better known and incorporated into the dermatologist practice.[3,4]

Wound healing

Wound healing is a complex and dynamic process dependent on the coordinated activity of multiple cells. It consists of three overlapping phases: the initial inflammatory (or migration) phase, lasting a few days, during which cytokines and growth factors recruit inflammatory cells; the proliferative (or mitotic) phase, lasting few weeks and characterized by the formation of granulation tissue, composed of fibroblasts that synthesize the extracellular matrix and by myofibroblasts that initiate contraction; and the final stage of maturation, lasting about seven months, which begins when the wound is closed. At this stage, the scar begins to retract and the edema decreases, the inflammatory cells gradually reduce in number, the extracellular matrix is degraded, the angiogenesis ceases, and the type III (immature) collagen is modified in type I (mature) collagen.[1,3]

Wound healing is an imperfect process, which can lead to elevated (hypertrophic and keloid) scars, hyperpigmented, and unsightly in appearance. Some factors influence the wound disfigurement, such as location, prolonged inflammation, infections, epithelialization delay, action of pericicatricial tissue, and tension forces of the adjacent skin.[1,3]

Aesthetic improvement of the scar

Studies in animals have shown that botulinum toxin type A injection in low doses could significantly improve the appearance of facial scars, as it would have an inhibitory action on the proliferation of the fibroblasts and, therefore, on the collagen production in a dose-dependent manner, reducing the appearance of retractions and improving the scar pattern. However, at high doses, it would have a negative effect by inhibiting the reepithelialization and decreasing the local angiogenesis.[1, 5, 6]

Also, the tension around the surgical scar is one of the most relevant factors in determining the final aesthetic outcome. This tension, in turn, is caused by the contraction of the local musculature. Usually, incisions are planned to follow the lines of force in parallel, but this is not always possible: thus it's interesting to use other techniques to reduce possible unaesthetic effects. Microtraumas caused by stress also induce prolonged inflammation, with increased metabolic activity and extracellular collagen and glycosaminoglycans deposition, leading to hypertrophic scars.[6 ,7, 8]

The application of botulinum toxin type A can be performed intraoperatively. One study demonstrated that the combination of botulinum toxin, anesthetic, and vasoconstrictor optimizes the botulinum toxin effect, resulting in earlier paralysis of the treated site. Botulinum toxin type B can also be applied, having a faster effect.[9]

Another study in primates observed, through standardized incisions, that the scars in the group treated with botulinum toxin had a positive esthetic result compared with the scars in the control group.[10] There is also in the literature a case report of patients who wished aesthetic improvement of a prior scar, performing a scar excision and intraoperative application of botulinum toxin, with a very satisfactory aesthetic result. Within three days, the surrounding musculature was paralyzed with minimal tension and distention from the wound margin.[6, 9] In another study, analyzing the thyroidectomy procedure scars of 30 patients, individuals in the group that received local botulinum toxin injection were more satisfied with the results than those that received saline injections. The scars treated with botulinum toxin type A became narrower, with natural coloring, and better overall appearance in the six months follow-up.[11]

Hypertrophic scar and keloids

Keloids and hypertrophic scars (HS) are caused by hyper-

proliferation of fibroblasts, resulting in excess collagen deposition. They are disfiguring and are often associated with clinical symptoms such as pruritus, pain, limited range of motion, contracture, and psychological effects on patients. Conventional options for the treatment of hypertrophic scars and keloids include intralesional injections of corticosteroids and 5-fluorouracil, surgery, cryotherapy, radiotherapy, laser therapy, and topical silicone gel sheets application. Recently, the use of botulinum toxin has been studied to treat symptoms and to prevent the formation of keloid and hypertrophic scars.[1, 12]

A recent study has reviewed the literature related to the subject and concluded that published clinical trials showed promising results demonstrating that botulinum toxin type A can modulate the development of keloids and hypertrophic scars. There appears to be scientific evidence that botulinum toxin type A negatively regulates TGF-b expression, reducing fibroblast proliferation and modulating collagen activity in pathological healing. However, keloid scars appear to be more resistant than hypertrophic scars to botulinum toxin type A therapy. Nevertheless, further studies are needed to more objectively define the applicability of this therapy.[12, 13, 14, 15]

Microdoses of botulinum toxin

The "microbotox" technique or microdoses of botulinum toxin application was developed by Wu in 2000 to provide more natural effects to patients. It is based on multi-point injection of highly diluted botulinum toxin every 0.8-1.0 cm into the dermis or at the between the dermis and the superficial layer of facial muscles.[1]

The main applications of this technique are to improve the appearance of fine lines and wrinkles by acting on the superficial muscles that insert into the skin. The use of the highly diluted botulinum toxin in small amounts at each injection prevents diffusion to deeper muscles, preventing a more frozen expression. Also, it has the advantage of reducing sweat production and the activity of the sebaceous glands, improving the appearance of the skin.[1, 16, 17, 18]

Lower face and neck region: When botulinum toxin is applied in microdoses in the anatomical region of the platysma muscle, it is observed an improvement in the neck skin texture and a decrease in the activity of the superficial fibers of this muscle, creating a "lifting" effect of the jowl and jaw areas, as well as a better cervical and mentalis muscle contour. This technique is indicated for patients with mild flaccidity of the cervical region, i.e., with early signs of aging that do not yet have an indication of surgery.[16]

This technique uses 20 units of 1 ml of saline solution for the preparation of microdoses of botulinum toxin. Two to three syringes containing 1 ml of the solution are used, and of each 1 ml syringe, about 100 to 120 microinjections should be performed. For the injection, the patient should be placed in a semi-reclined position, with the chin raised, keeping the skin stretched. Bleaching of the skin with the formation of papule should be observed at the time of the injection. A slight resistance should be felt when pressing the plunger: if the solution is easily injected, the needle was probably inserted very deeply.[16]

"Accordion wrinkles": Patients with significant photoaging and loss of volume may develop multiple parallel fine lines of varying depth ranging from the orbital region to the cervical region, which lead to the aspect of "scratch face" or "accordion lines". These wrinkles are more apparent when smiling, but over time they can become static. Its treatment is challenging due to the superficiality and length of the lines. The technique of multiple superficial injections of highly diluted botulinum toxin with or without hyaluronic acid (for skin hydration) may be employed, with a maximum of 40 units per side recommended. The effect on treated patients was a significant improvement in "accordion wrinkles" and skin appearance.[17, 18]

The microdoses of botulinum toxin technique is a new tool that has proven to be effective in treating some wrinkles and facial aging. However, a qualified professional should perform it since there is a risk of inadvertently paralyzing the deeper musculature of the treated area.

Scrotal rejuvenation

Scrotal wrinkling can also be referred to as scrotal rugosum or cutis scrotum gyratum. Some patients have excessive scrotal wrinkling and feel embarrassed at the time of sexual intercourse. The contraction of the dartos muscle, a rugated fascial muscle of the scrotum, in response to cold temperatures or sexual intercourse may result in the accentuation of scrotal wrinkling. As the contraction of the dartos muscle is a contributing component to the etiology of scrotal wrinkling, the botulinum toxin injection can result in a smoother, less wrinkled skin surface. There is no well-defined application protocol on the scrotal rejuvenation technique with botulinum toxin.[19]

Muscle definition

With the evolution of the modalities of botulinum toxin application, its extrafacial use has been gaining prominence, mainly in Asia. Oriental women tend to have shorter legs and when there is hypertrophy of the gastrocnemius muscle, the feeling of "stubby" legs is increased, which is considered an obstacle to beauty for the aesthetic standards of Asians, who seek more elongated legs, unlike Westerners. Botulinum toxin has been used as a noninvasive way of achieving this goal. It is applied to the medial head of the gastrocnemius muscle, which is the most prominent and functionally redundant calf muscle.

Bogari *et al.* demonstrated, through a three-dimensional magnetic resonance imaging study, that the most effective technique consists of the botulinum toxin application in 48 points, distant about 2 cm apart, at a dose of 1.5 UI at each point. The technique results in an effective reduction of the circumference of this leg region, giving the impression of a more elongated lower limb. It is important to emphasize that this technique can be used in thin patients, where the calf diameter is primarily due to gastrocnemius hypertrophy. Also, it should be used with caution as it may result in gait abnormalities and fatigue after walking or running. In this technique, the muscle decreases to approxima-

tely half of its original volume after five to six months, returning to its original volume 10-12 months after the injection.[20]

If the individual avoids active exercise of the treated muscle, the return to muscle volume pre-treatment can be prevented. Clinical experience indicates that repeated injections over several years may also result in chronic muscular atrophy.[20, 21, 22]

Non-aesthetic uses

The main use of botulinum toxin in Dermatology is related to facial aesthetics. In recent years, however, the botulinum toxin use in dermatological diseases with good results has been observed.[1] Several diseases nowadays find in botulinum toxin a differentiated option, whose effectiveness is being increasingly studied and proven, enabling dermatologists to offer new therapeutic options to their patients.[1, 3]

Rosacea

Rosacea is an inflammatory skin disease, with chronic and relapsing evolution, which presents clinically persistent facial erythema, papules, pustules, telangiectasias, and recurrent flushing. Its symptoms can cause embarrassment, low self-esteem, anxiety, worsening the quality of life of patients. Its treatment is challenging because, in general, symptoms respond only partially to traditional therapies, and the tendency for recurrence is significant. Given this picture, the use of intradermal botulinum toxin has been investigated as a new therapy. It would block the release of the neurotransmitter acetylcholine from the periphery of the nerves with reduction of cutaneous vasodilation and consequent reduction of facial erythema and flushing.[23, 24, 25]

Many studies have been published showing the benefits of botulinum toxin in rosacea treatment. One of the most recent studies assessed two Korean women with resistant symptoms of erythema and facial flushing and obtained satisfactory results. For the treatment, 50 UI of botulinum toxin was diluted in 2.5 ml of sterile saline, resulting in a concentration of 2 UI for every 0.1 ml of the solution. Intradermal botulinum toxin injections were applied vertically at a 90° angle at marked points every 1 cm in the entire erythema area, exceeding 1 cm of this area. Two sessions were held, with intervals of one week between them. In the first session, most of the product was applied, and in the second, it was applied only in the areas of remaining erythema.[25]

The mesotherapy is another form of botulinum toxin application, also presenting positive results. Bharti *et al.* described the intradermal botulinum toxin injection (10 U/mL) as 0.05 mL microdroplets in the central region of the face. The injections are spaced every 0.5 cm and applied under topical anesthesia. Improvement in erythema, edema, telangiectasia, and flushing was observed within one to two weeks, and this improvement lasted approximately three to four months when it was necessary to repeat the treatment.[26]

In 2017, Dayan *et al.* conducted a randomized double-blind study in which patients receiving botulinum toxin injections presented a significant reduction in the primary characteristics of rosacea at four weeks post-treatment, while the group receiving the same volume of injection with saline solution showed no improvement.[27] These new findings demonstrate that botulinum toxin can be considered a safe and effective agent to reduce the severity and symptoms of rosacea, in addition to increasing patient satisfaction.

Decreased acne/ sebum production

In recent years, several studies have shown promising results of the botulinum toxin use to improve skin oiliness and, consequently, acne. The results of recent publications have indicated a significant reduction in sebum production and have demonstrated a correlation between sebum production and injection techniques, although the dosage used is unknown. There is also evidence to suggest that the action of acetylcholine on the muscarinic receptor is an important regulator of sebum production.[1]

Shah published one of the first reports in the literature in 2008 where 20 patients were evaluated after the intradermal administration of botulinum toxin in the "T zone". A significant photographic improvement after one month of treatment was observed in skin oiliness, as well as a decrease in pore size in 17 of the 20 patients analyzed.[28]

Subsequently, Rose & Goldberg applied intradermal botulinum toxin in the frontal region of 25 patients, obtaining results that suggest that botulinum toxin reduces the sebum production in patients with oily skin, with a high degree of satisfaction.[29]

In 2015, Min *et al.* conducted the first prospective, randomized, double-blind study in 42 female patients to assess the amount of sebum in the frontal region of individuals treated with intramuscular botulinum toxin. In fact, the study confirmed the reduction of sebum excretion around the region of application of 2 UI of botulinum toxin without the benefit of larger doses (4UI). However, away from the injection site, the sebum production gradually normalized, even increasing in areas without botulinum toxin, perhaps by a compensatory mechanism. Sebum production was recovered after 16 weeks of follow-up. Additionally, although it was not the objective of the study, a reduction in the pore size in these patients was also observed.[30]

Craniofacial hyperhidrosis

Hyperhidrosis is defined as excessive sweating, being a common symptom in the population, and causing psychological and social problems. Craniofacial hyperhidrosis can affect only the face and scalp, or be part of a genetically engineered hyperhidrosis, often involving multiple sites of the skin. Botulinum toxin type A is well established in the treatment of hyperhidrosis in other sites. In the case of craniofacial hyperhidrosis, botulinum toxin type B, which is not widely used for this purpose, could be advantageous, as it would act less on motor neurons, thus preventing eyebrows hair loss.[31]

Karlgvist *et al.* used botulinum toxin type B to treat facial and scalp hyperhidrosis in 42 patients, finding a positive result in the reduction of sweat production and mainly in patients' quality of life. The treatment used 5 UI of intradermal botulinum toxin type B injection, spaced 15 mm between the points of applica-

tion throughout the hyperhidrosis area, sparing the forehead area distant less than 4 cm from the eyebrow. Of the treated patients, 18% complained of temporary forehead stiffness and eyebrows hair loss; nevertheless, most of these patients returned later for new applications due to the hyperhidrosis improvement.[31]

Another study reported the use of botulinum toxin type A in 11 female patients with postmenopausal craniofacial hyperhidrosis. Intradermal botulinum toxin injections of 0.1 ml (25 UI/ml concentration) were performed in the areas to be treated and 64% of the patients perceived complete response in their symptoms with no observed adverse events.[32]

Fox-Fordyce disease

Nowadays, given its already established use and its new applicability, botulinum toxin has been considered a therapeutic possibility for other skin diseases. Fox-Fordyce disease is characterized by intensely pruritic papules in the regions of the apocrine glands, for which there is currently no definitive treatment or a known cure. In 2016, a 52-year-old female patient with this disease was treated with intradermal botulinum toxin type A injections, 2 UI, every 2 cm, totaling 100 UI for both armpits. After the treatment, the patient presented a marked reduction in the size and number of axillary papules, as well as a complete improvement of the local pruritus. This case showed that botulinum toxin type A might be considered a therapeutic option for recalcitrant Fox-Fordyce disease. However, clinical trials are still necessary to assess the best treatment modalities for this disease.[33]

Hailey-Hailey's Disease

Hailey-Hailey's disease (HHD), also known as familial benign chronic pemphigus, is an unusual bullous dermatosis whose anatomopathological feature is characterized by suprabasal acantholysis, giving the epidermis the appearance of a "dilapidated brick wall". Clinically, it presents flaccid blisters, painful erosions, and fissures in the intertriginous regions, especially in the axillary and inguinal areas. The disease has a recurrent course and is often complicated by a secondary infection. Traditional treatments for Hailey-Hailey's disease include oral and topical antibiotics and corticosteroids, cyclosporin, dapsone, and methotrexate for patients with recalcitrant disease. However, none of these agents provides long-term relief for most patients, urging to seek other therapies. As Hailey-Hailey's disease is exacerbated by sweat, friction, and heat, botulinum toxin type A has been identified as useful for the treatment of this disease in the recent literature, since its injections result in denervation of the sweat glands, with reduction of sweating and less chance of maceration, consequently preventing the development of secondary infections.[1, 34, 35, 36]

Studies have shown that the use of botulinum toxin type A resulted in marked improvement and long-term remission of the disease, with the advantage of being easy to apply and having few adverse events. Some authors even suggest that currently it could be considered the first line of treatment after failure with topical corticosteroids and antimicrobials use.[34, 35, 36] It is recommended to use 100 IU to 200 IU of botulinum toxin type A in the affected sites, with an average of approximately 50 IU per armpit or groin. A 100 UI vial of botulinum toxin can be reconstituted in 4 mL of saline, reaching a dilution of 2.5 UI for every 0.1 mL of solution.[35]

Psoriasis

Inverse psoriasis affects especially the flexural areas, and is characterized by erythematous, exulcerated, and infiltrated plaques associated with local burning sensation and pruritus. Some studies and case reports have shown that botulinum toxin could be a therapeutic option for inverse psoriasis by reducing local sweating and, consequently, maceration and infection. Also, it was believed that it would inhibit neuropeptides, reducing inflammation and pain transmission.[1,2]

Zanchi *et al*. demonstrated the first favorable results with botulinum toxin use in a study with 15 patients with inverse psoriasis who were treated with injections of 2.4 UI of botulinum toxin, placed 2.8 cm apart from each other, totalizing 50 UI or 100 UI of toxin per patient. Improvement in erythema extent and infiltration intensity was observed in 87% of patients and maintained for 12 weeks after treatment. Due to these findings, because it acts in controlling inflammation and substances involved in the mechanism of inverse psoriasis, botulinum toxin may become a new option in inverse psoriasis treatment.[37]

In the treatment of plaque psoriasis, studies show less positive results. Bagherani *et al*. conducted the first double-blind randomized study to assess the efficacy of botulinum toxin in the treatment of plaque psoriasis. Twenty subjects were recruited, from which two psoriasis plaques were selected: in one, a saline solution was applied, and in the other, a total of nine injections of 4 UI of botulinum toxin type A was applied at each point. The treated plaques were reassessed after one, three, four and eight weeks of treatment but did not achieve a statistically significant improvement over the control group.[38] However, in our review, we found a case report demonstrating a sustained local improvement of a psoriasis plaque in a patient after a single injection of intradermal botulinum toxin.[39]

Thus, while the results, for the time being, are discouraging, further studies on the subject may still be necessary.

Notalgia paraesthetica

It is known that botulinum toxin inhibits the presynaptic release of acetylcholine and that acetylcholine mediates pruritus in atopic dermatitis. Additionally, the toxin also inhibits substance P and glutamate, probably involved in pruritus. Thus, botulinum toxin stands out as a possible therapeutic option for pruritic conditions.[40]

Notalgia paraesthetica is chronic sensory neuropathy that affects the interscapular area, characterized by local pruritus and hyperpigmentation of the region. Other associated symptoms are pain, paresthesia, hypoesthesia, hyperesthesia, and burning sensation. Usual treatments for this condition include local anesthesia, topical corticosteroids, and capsaicin. However, none of these shows good results and long-term efficacy.[41]

In 2007, Weinfeld proposed that botulinum toxin would

be an effective and safe treatment for notalgia paraesthetica. The author performed intradermal botulinum toxin injections of 4UI in the affected area, placed 2 cm apart from each other, in two patients followed for 18 months. They showed a significant improvement in local pruritus and hyperpigmentation in the long term.[41] Wallengren and Bartosik also reported improvement in pruritus in four patients with notalgia paraesthetica treated with botulinum toxin.[40]

On the other hand, Pérez *et al.*, in treating five patients with notalgia paraesthetica, found that improvement in pruritus varied in each case, but that no patient presented a complete resolution of the condition or improvement of the brownish spot.[42] Maari *et al.* also showed no improvement of pruritus and hyperpigmentation in notalgia paraesthetica when comparing treatment with botulinum toxin type A (10 patients) and placebo (10 patients).[43] Therefore, due to divergences in the literature, the benefits of botulinum toxin for this condition are debatable, requiring further studies.

Postherpetic neuralgia and other pain syndromes

Postherpetic neuralgia (PHN) is one of the most formidable adverse events of herpes zoster, which mainly affects elderly and immunocompromised populations. Neuralgia can be explained by the increase in the number of P nerve fibers at the site of infection and reduction in the number of large nerve fibers responsible for inhibiting the painful stimulus.[44, 45] The mechanism of action of botulinum toxin in pain relief is not fully understood; however it is believed to act by inhibiting the release of pain mediators, such as glutamate, substance P, and calcitonin gene-related peptide in the dorsal root ganglia, reducing inflammation around the nerve endings, deactivating the sodium channels, and inhibiting axonal transport.[46, 45]

One study investigated the effect of botulinum toxin on 58 patients presenting postherpetic neuralgia symptoms for four to 15 months. In this study, botulinum toxin was effective in reducing pain in 18 (31%) cases and showed significant results in 27 (46.6%) cases. However, it was ineffective in the remaining 13 (22.4%) patients. The severity of pain, frequency, and duration of events was significantly reduced after treatment.[47]

In a recent review study, level A evidence (effective) was observed not only for postherpetic neuralgia treatment but also for trigeminal and posttraumatic neuralgia.[48] Fischoff *et al.* concluded in their review that there is a moderate level of evidence on the efficacy of the botulinum toxin use for the treatment of trigeminal neuralgia and postherpetic neuralgia.[49]

Emad *et al.* assessed the efficacy of botulinum toxin in 15 patients with postherpetic neuralgia by injecting 15 IU per 10 cm^2 of affected area, obtaining improvement of pain in all patients, although the analgesic effect diminished over the weeks.[44] Xiao *et al.* compared the use of botulinum toxin over placebo and achieved a significant improvement in pain and sleep in patients treated with the toxin presenting symptoms of postherpetic neuralgia.[46] Another study, assessing 30 patients, also showed the efficacy of botulinum toxin over placebo in postherpetic neuralgia treatment, as well as its tolerability and safety.[50]

The application should be performed at points in the area of pain delimited by the patient, distant 1cm between each other, in the amount of 0.5-1 IU per point.

Despite the current advancement of treatments, postherpetic neuralgia persists in many individuals influencing their daily activities and reducing their quality of life. Many commonly used treatments present adverse events and should be used with caution in the elderly or in patients with multiple comorbidities. In this context, botulinum toxin presents as an interesting therapeutic alternative.

Raynaud's Disease

Raynaud's disease, or Raynaud's phenomenon (RP) is a vasospastic disorder of digital vessels, triggered by exposure to cold or stress. It is more commonly observed in the hands, but it also frequently affects the toes.[51] Botulinum toxin has been presented as a treatment modality for Raynaud's disease, being increasingly studied.[52]

In a review study on the use of botulinum toxin in Raynaud's disease, Zhou *et al.* concluded that botulinum toxin acts on vascular smooth muscle blocking norepinephrine transmission and preventing vasoconstriction, in addition to blocking alpha-adrenergic receptors leading to the reduction of cold-induced vasoconstriction, as well as pain.[52]

Dhaliwak *et al.* demonstrated the treatment of three patients with severe Raynaud's disease in the feet treated with 10 UI of botulinum toxin injected at the base of each toe, evolving with improved cold tolerance, color change, frequency and severity of the episodes six weeks after the application, with a duration of about five months.[51]

Patients with digital ulcers resulting from severe cases of Raynaud's disease may also benefit from the use of botulinum toxin. Studies have shown, through angiography, improved blood flow, with scarring of ulcers after the application of toxin.[53, 54]

Bello *et al.* performed a double-blind, controlled, clinical trial with scleroderma patients who received botulinum toxin applications in one hand and saline solution in the other. The study concluded that there should be some positive effect, but it was questionable as to its significance.[51]

The role of botulinum toxin in the treatment of Raynaud's disease should be more studied in populations of more homogeneous patients and in unique clinical situations, such as acute digital ischemia, to better elucidate its real efficacy and indication.[55]

Treatment of recalcitrant chronic pruritus

Localized chronic pruritus is a common symptom that significantly affects health and quality of life. Botulinum toxin showed potential as an antipruritic agent in patients with localized chronic pruritus, refractory to conventional therapies.[56]

Pruritus is driven by C nerve fibers, which are sensitive to neurotransmitters, histamine, and other inflammatory mediators, such as substance P and calcitonin gene-related peptide. A recent study showed that botulinum toxin is responsible for

reducing histamine-induced pruritus, as well as vasomotor reactions and neurogenic inflammation.[56] Other studies have shown that botulinum toxin reduces the release of glutamate, substance P, and calcitonin gene-related peptide.[57] Some studies indicate that botulinum toxin is an effective option in the treatment of lichen simplex chronicus, since pruritus is marked in this pathology.[58]

As the number of studies is limited, there is still insufficient evidence to reach a conclusion on the effectiveness of botulinum toxin in the treatment of chronic pruritus.

CONCLUSION

Botulinum is a simple, safe method with satisfactory results and is well established throughout the world for the treatment of facial wrinkles. Ongoing research is identifying the use of botulinum toxin for other purposes, both in the aesthetic and in the therapeutic field. This study aimed at conducting a literature review on these applications, possibly useful in the dermatologist practice.

In the aesthetic area, botulinum toxin has shown benefit in the treatment of hypertrophic scars, scrotal rejuvenation, definition of the gastrocnemius muscle, and in microdoses in the face and neck region. However, for the treatment and prevention of keloids, further studies are still necessary.

Moreover, in the treatment of dermatological disorders, this review showed that botulinum toxin might be useful for postherpetic neuralgia and other pain syndromes, craniofacial hyperhidrosis, rosacea, and Hailey-Hailey's disease.

Also, new studies show that its use could be extended to other diseases such as recalcitrant chronic pruritus, Raynaud's disease, notalgia paraesthetica, inverse psoriasis, and Fox Fordyce disease. However, clinical trials are necessary before these treatments become a clinical reality.[1]●

REFERENCES

1. Schlessinger J, Gilbert E, Cohen JL, Kaufman J. New Uses of AbobotulinumtoxinA in Aesthetics. Aesthet Surg J. 2017;37(suppl 1):s45-58.
2. Monheit GD, Pickett A. AbobotulinumtoxinA: A 25-Year History. Aesthet Surg J. 2017;37(suppl 1):4-11.
3. Antonio CR, Antônio JR, Trídico LA. Botulinum toxin: a review of its applicability in diseases within the reach of dermatologists. Surg Cosmet Dermatol. 2014;6(3):268-76.
4. Braz AV, Louvain D, Mukamal LV. Combined treatment with botulinum toxin and hyaluronic acid to correct unsightly lateral-chin depression. An Bras Dermatol. 2013;88(1):140-2.
5. Gugerell A, Kober J, Schmid M, Buchberger E, Kamolz LP, Keck M. Botulinum toxin A: Dose-dependent effect on reepithelialization and angiogenesis. Plast Reconstr Surg Glob Open. 2016;4(8):e837.
6. Jablonka EM, Sherris DA, Gassner HG. Botulinum toxin to minimize facial scarring. Facial Plast Surg. 2012;28(5):525-35.
7. Gassner HG, Sherris DA. Addition of anesthetic agent enhances the predictability of botulinum toxin injections. Mayo Clin Proc. 2000;75(7):701-4.
8. Wilson AM. Use of botulinum toxin type A to prevent widening of facial scars. Plast Reconstr Surg. 2006;117(6):1758-66.
9. Flynn TC. Use of intraoperative botulinum toxin in facial reconstruction. Dermatol Surg. 2009;35(2):182-8.
10. Gassner HG, Sherris DA, Otley CC. Treatment of facial wounds with botulinum toxin A improves cosmetic outcome in primates. Plast Reconstr Surg. 2000;105(6):1948-53.
11. Kim YS, Lee HJ, Cho SH, Lee JD, Kim HS. Early postoperative treatment of thyroidectomy scars using botulinum toxin: a split-scar, double-blind randomized controlled trial. Wound Repair Regen. 2014;22(5):605-12.
12. Austin E, Koo E, Jagdeo J. Commentary on The Cellular Response of Keloids and Hypertrophic Scars to Botulinum Toxin A: A Comprehensive Literature Review. Dermatol Surg. 2018;44(2):149-57.
13. 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.
14. Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. Plast Reconstr Surg. 2009;124(5):275-7.
15. 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.
16. Wu WTL. Microbotox of the lower face and neck: evolution of a personal technique and its clinical effects. Plast Reconstr Surg. 2015;136(5 suppl):92-100.
17. Môle B. Accordion wrinkle treatment through the targeted use of botulinum toxin injections. Aesthetic Plast Surg. 2014;38(2):419-28.
18. Môle B. Griffose faciale: traitement des rides dynamiques du visage par injections dermiques simultanées de toxine botulique A et d'acide hyaluronique. Ann Chir Plast Esthet. 2012;57(3):194-201.
19. Cohen PR. Scrotal Rejuvenation. Cureus. 2018;10(3):2316.
20. Bogari M, Tan A, Xin Y, Chai G, Lin L, Min P, et al. Treatment of Gastrocnemius Muscle Hypertrophy with Botulinum Toxin Injection Followed by Magnetic Resonance Imaging Assessment and 3-Dimensional Evaluation. Aesthet Surg J. 2017;37(10):1146-56.
21. Seo KK, Lee W. Medytoxin/Neuronox®. In: Carruthers J CA, ed. Botulinum Toxin. Philadelphia, Pa.: Elsevier; 2012.10.52-8.
22. Wu WT. Facial and lower limb contouring. In: Benedetto A, ed. Botulinum Toxins in Clinical Aesthetic Practice. Boca Raton: CRC Press; 2011.p.206-22.
23. Friedman O, Koren A, Niv R., Mehrabi JN, Artzi O. The toxic edge-A novel treatment for refractory erythema and flushing of rosacea. Laser Surg Med. 2019;51(4):325-31.
24. Abokwidir M, Feldman SR. Rosacea Management. Skin Append Disord. 2016;2(1-2):26-34.
25. Park KY, Hyun MY, Jeong SY, Kim BJ, Kim MN, Hong CK. Botulinum Toxin for the Treatment of Refractory Erythema and Flushing of Rosacea. Dermatology. 2015; 230(4):299-301.

26. Bharti J, Sonthalia S, Jakhar D. Mesotherapy with Botulinum toxin for the treatment of refractory vascular and papulopustular rosacea. J Am Acad Dermatol. 2018. doi: 10.1016/j.jaad.2018.05.014. [Epub ahead of print]
27. Dayan SH, Ashourian N, Cho K. A Pilot, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of IncobotulinumtoxinA Injections in the Treatment of Rosacea. J Drugs Dermatol. 2017;16(6):549-54.
28. Shah AR. Use of intradermal botulinum toxin to reduce sebum production and facial pore size. J Drugs Dermatol. 2008;7(9):847-50.
29. Rose AE, Goldberg DJ. Safety and Efficacy of Intradermal Injection of Botulinum Toxin for the Treatment of Oily Skin. Dermatol Surg. 2013;39(3pt1):443-8.
30. Min P, Xi W, Grassetti L, Trisliana PA, Torresetti M, Feng S, et al. Sebum Production Alteration after Botulinum Toxin Type A Injections for the Treatment of Forehead Rhytides: A Prospective Randomized Double-Blind Dose-Comparative Clinical Investigation. Aesthet Surg J. 2015;35(5):600-10.
31. Karlqvist M, Rosell K, Rystedt A, Hymnelius K, Swartling C. Botulinum toxin B in the treatment of craniofacial hyperhidrosis. J Eur Acad Dermatol Venereol. 2013; 28(10):1313-17.
32. Eustace K, Wilson NJ. Postmenopausal craniofacial hyperhidrosis. Clin Exp Dermatol. 2017;43(2):180-2.
33. González-Ramos J, Alonso-Pacheco ML, Goiburú-Chenú B, Mayor-Ibarguren A, Herranz-Pinto P. Successful treatment of refractory pruritic Fox-Fordyce disease with botulinum toxin type A. Br J Dermatol. 2015;174(2):458-9.
34. Farahnik B, Blattner CM, Mortazie MB, Perry BM, Lear W, Elston DM. Interventional treatments for Hailey-Hailey disease. J Am Acad Dermatol. 2017;76(3):551-8.
35. Kothapalli A, Caccetta T. Botulinum toxin type A for the first-line treatment of Hailey-Hailey disease. Austral J Dermatol. 2018;60(1):73-4.
36. Rezende BG, Corsetti GT, Manzoni AP, Weber MB, Bonamigo RR. Hailey-Hailey disease treatment with Botulinum toxin type A. An Bras Dermatol. 2010;85(5):717-22.
37. 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.
38. Bagherani N, Smoller BR. The efficacy of botulinum neurotoxin A in the treatment of plaque psoriasis. Dermatol Ther. 2018;31(2):e12587.
39. Gilbert E, Ward NL. Efficacy of botulinum neurotoxin type A for treating recalcitrant plaque psoriasis. J Drugs Dermatol. 2014;13(11):1407-8.
40. Wallengren J, Bartosik J. Botulinum toxin type A for neuropathic itch. Br J Dermatol. 2010;163(2):424-6.
41. Weinfeld PK. Successful treatment of notalgia paresthetica with botulinum toxin type A. Arch Dermatol. 2007;143(8):980-2.
42. 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.
43. 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.
44. 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.
45. Shrestha M, Chen A. Modalities in managing postherpetic neuralgia. Korean J Pain. 2018;31(4):235-43.
46. 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.
47. Ding XD, Zhong J, Liu YP, Chen HX. Botulinum as a Toxin for Treating Post-herpetic Neuralgia. Iran J Public Health. 2017 May; 46(5):608-611.
48. 48. Safarpour Y, Jabbari B. Botulinum toxin treatment of pain syndromes - an evidence based review. Toxicon. 2018;147:120-8.
49. Fischoff D, Spivakovsky S. Botulinum toxin for facial neuralgia. Evid Based Dent. 2018;19(2);57-8.
50. 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.
51. Dhaliwal K, Griffin M, Denton CP, Butler PEM. The novel of botulinum toxin A for the treatment of Raynaud's phenomenon in toes. BMJ Case Reports. 2018. doi: 10.1136/bcr-2017-219348. [Epub ahead of print]
52. Zhou Y, Liu Y, Hao Y, et al. The mechanism of botulinum A on Raynaud syndrome. Drug Des Devel Ther. 2018;12:1905-15.
53. Motegi SI, Sekiguchi A, Saito S, Ishibuchi H, Kishi C, Yasuda M, et al. Successful treatment of Raynaud's phenomenon and digital ulcers in systemic sclerosis patients with botulinum toxin B injection: Assessment of peripheral vascular disorder by angiography and dermoscopic image of nail fold capillary. J Dermatol. 2018;45(3):349-52.
54. Garrido-Ríos AA, González-Olivares M, Navarro-Vidal B, Martínez-Morán C, Borbujo J. Ischaemic ulcers on the toes secondary to Raynaud phenomenon in a patient with systemic sclerosis successfully treated with botulinum toxin. Clin Exp Dermatol. 2018;43(4):503-5.
55. Bello RJ, Cooney CM, Melamed E, Follmar K, Yenokyan G, Leatherman G, et al. The Therapeutic Efficacy of Botulinum Toxin in Treating Scleroderma-Associated Raynaud's Phenomenon: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Arthritis Rheumatol. 2017;69(8):1661-9.
56. Boozalis E, Sheu M, Selph J, Kwatra SG. Botulinum toxin type A for the treatment of localized recalcitrant chronic pruritus. J Am Acad Dermatol. 2018;78(1):192-4.
57. Han SB, Kim H, Cho SH, Chung JH, Kim HS. Protective effect of Botulinum Toxin type A against atopic dermatitis-like skin lesions in NC/Nga Mice. Dermatol Surg. 2017;43 (Suppl 12):S312-21.
58. 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

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