

New trends in botulinum toxin use in dermatology

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Key words: botulinum toxin, BoNT-A, dermatology, hyperhidrosis, scars

Citation: Guida S, Farnetani F, Nisticò SP, Giorgio Mariarosaria C, Babino G, Pellacani G, Fulgione E. New trends in botulinum toxin use in dermatology. *Dermatol Pract Concept*. 2018;8(4):277-282. DOI: <https://doi.org/10.5826/dpc.0804a05>

Received: March 10, 2018; **Accepted:** May 28, 2018; **Published:** October 31, 2018

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Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

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ABSTRACT **Background:** Recent studies have highlighted new botulinum neurotoxin (BoNT) applications in the field of dermatology.

Objective: To review current knowledge of BoNT use in dermatology.

Methods: The literature of the last 5 five years has been reviewed.

Results: We describe interesting protocols of BoNT treatment for hyperhidrosis (HH), hypertrophic scars and keloids, Raynaud phenomenon, facial flushing, oily skin, psoriasis, Hailey-Hailey disease, and cutaneous lesions like painful lesions and periorbital syringomas.

Conclusions: Several skin conditions eligible for BoNT treatment have been described. After the wide application for HH treatment, scars as well as vascular and inflammatory skin disorders, oily skin and cutaneous lesions represent fields of application of BoNT.

Introduction

The botulinum neurotoxin (BoNT) is produced by *Clostridium botulinum* bacteria. Seven toxin isoforms can be distinguished (BoNT A-G) [1,2], with BoNT-A and B being commercially available for clinical applications. Both BoNT-A and BoNT-B are proteins composed of a heavy and a light chain. These chains are related to the mechanism of action of the toxin. Accordingly, the heavy chain binds the BoNT to

the cholinergic nerve terminal while the light chain inhibits the release of acetylcholine from presynaptic vesicles [3,4]. The difference between BoNT-A and B is the type of protein the light chain cleaves and different procedures in which they are employed [5].

In 1989, BoNT, onabotulinumtoxinA, was initially approved for the treatment of strabismus and blepharospasm by the US Food and Drug Administration (FDA). Lately, aesthetic indications have been progressively intro-

duced and the popularity of BoNT-A has increased 6956.6% from 1997 to 2016 [6].

The most recognized mechanism of action of BoNTs is the inhibition of neurotransmitters (acetylcholine, norepinephrine, substance P, calcitonin gene-related peptide [CGRP], and glutamate) release at the presynaptic neuromuscular junction. However, BoNTs can affect both sympathetic and parasympathetic functionality since acetylcholine is also a neurotransmitter of the autonomic nervous system [7]. Furthermore, recent evidence shows the effect of BoNTs on different human cell types, both neuronal and non-neuronal cells. These latter include epidermal keratinocytes, mesenchymal stem cells from subcutaneous adipose, neutrophils and macrophages, dermal fibroblasts, mast cells, sebocytes and vascular endothelial cells. Thus, several clinical applications are emerging in dermatology [2,8]. The aim of this article is to review new trends in BoNT treatment in dermatology.

Methods

Studies focusing on the use of BoNT in dermatology were retrieved from PubMed. We discovered 327 articles, from 2012 to December 2017, using the terms “botulinum toxin dermatology” and correlated MeSH terms (“botulinum toxins”[MeSH Terms] OR (“botulinum”[All Fields] AND “toxins”[All Fields]) OR “botulinum toxins”[All Fields] OR (“botulinum”[All Fields] AND “toxin”[All Fields]) OR “botulinum toxin”[All Fields] AND (“dermatology”[MeSH Terms] OR “dermatology”[All Fields])). Of these articles, only 54 were included in this review. Exclusion criteria were: case reports, duplicated studies, papers focusing on other topics (ie, aesthetics, neurology), and articles written in languages other than English.

Results

Hyperhidrosis

Hyperhidrosis (HH) is a skin condition characterized by excessive secretions of the eccrine glands located, above all, at the palms, soles and axillae, and it affects approximately 3% of the population. Thus treatment of hyperhidrosis with BoNT represents one of the most widespread applications of the BoNT. BoNT is injected intradermally in order to target sweat gland function through the inhibition of neurotransmission at nerve terminals reaching the glands [9-11].

Several issues regarding BoNT treatment have been addressed in the last few years. In detail, BoNT has been compared to other available treatment modalities. Treatment options should be carefully evaluated and selected for each patient [7,12-16]. However, BoNT has been proven to be effective in reducing the severity of HH and to improve

quality of life (QoL) of HH patients. Accordingly, a profound QoL impairment is experienced by these patients, although no anxiety, depression or excessive alcohol consumption has been associated with the disease [17].

Both adults and children can benefit from BoNT-A and B treatment [4,18,19].

Specifically, BoNT-B seems to be the treatment of choice in patients with multifocal HH since it can be used to treat multiple sites in the same session, thus improving QoL [4].

In pediatric patients, HH affects 1.6% of adolescents and 0.6% of prepubertal children [20], and it remains widely undertreated. However, BoNT has been demonstrated to be effective and safe [21]. A multicenter, nonrandomized, open-label study of onabotulinumtoxinA treatment (50 IU per axilla) of bilaterally primary axillary HH in adolescents from 12 to 17 years old showed an improvement of 75% in 79.4-93.2% patients [22]. The efficacy of BoNT treatment has been proven for axillary HH by several randomized trials in the past. Therefore, BoNT for HH of the axillae is FDA-approved, but it has also been reported effective for the treatment of other sites. Palmar HH, for instance, is usually treated with 100–200 IU. Pain can limit this treatment; thus several strategies have been evaluated to increase the compliance. Among these, ice with pressure, ice <20 or >20 seconds associated or not with topical anesthesia [23,24], general anesthesia, nerve blocks, vibration, pressure [21], and needle-free injections (Med-Jet MBX, Medical International Technologies, Montreal, QC, Canada) [25]. However, an open-label prospective study involving 20 patients with palmar HH, treated with needle injection on the right hand and with a needle-free device, has proven the efficacy of the device to be lower as compared to the classic needle injection [25].

Repeated injection protocols have been proposed for both axillary and palmar treatment, in 3 different retrospective studies [26-28]. Repeated injections have been demonstrated to increase the duration of the effect from 5.5 to 8.5 months with 125 IU of abobotulinumtoxinA *per* underarm while it passed from 4 to 5 months when 50 U of onabotulinumtoxinA *per* axilla were employed [26, 27]. The median duration of efficacy for palmar repetitive treatment was 7 months for the first injection and 9.5 months for the last with 250 IU of abobotulinumtoxinA *per* palm [28]. Palmar treatment should be performed carefully on the thenar eminence, as there is a risk of inducing weakness of the hand. On the other hand, repeated injections can be related to the development of neutralizing antibodies. Nevertheless, a 3-month interval between each injection has not been related to the presence of these antibodies [26,28].

Data concerning plantar treatment with BoNT are scarce [29]. Doses employed vary from 50 to 250 IU of onabotulinumtoxinA *per* plantar area with effects lasting 3–6 months [30].

Indications for HH involving other cutaneous sites and osmidrosis treatment have also been described [31-36].

Hypertrophic Scars and Keloids

BoNT treatment has been proposed for the treatment of hypertrophic scars and keloids [37,38]. Tension due to motion is a well-known factor in determining scar tissue hypertrophy [39]. Thus, the ability of BoNT to reduce muscle contraction in the scar area can result in a decrease of skin tension, microtrauma, and subsequent inflammation [39]. Another underlying biological mechanism that has been hypothesized is the contribution in reducing the expression of transforming growth factor beta, the main regulator of hypertrophic scar formation [40]. Injection of BoNT may vary from 17.5–40 IU of onabotulinumtoxinA. BoNT can be employed either at the site of scar formation or suture removal [41].

A split-scar, double-blind randomized controlled trial involving 15 patients with early post-thyroidectomy scars revealed a significant improvement in one half of the scar, corresponding to the BoNT-treated area, as compared to the other part injected with 0.9% saline solution. Treatments were performed within 10 days after the surgery and evaluations were performed after 6 months [42].

Keloids are commonly managed with intralesional corticosteroids. A recent randomized controlled trial enrolled 24 patients with keloids randomly treated with intralesional steroids and BoNT-A. Both treatments were effective in reducing the volume and height of lesions and increasing their softening. Nevertheless, BoNT was more effective in reducing itching and pain related to keloids [43]. However, 3D profilometry used to objectively evaluate BoNT-A-treated keloids revealed the absence of results in some cases. This clinical observation has been supported by studies showing no TGF beta or fibroblast variations after BoNT treatment of scars. Consequently, contradictory results from a clinical and biological point of view are available at the moment, and further well-designed studies are necessary to evaluate the real role of BoNT in the scarring process [5].

Raynaud Phenomenon

Raynaud phenomenon (RP) consists of severe vasospasms leading to pain and digital ulceration, thus impairing daily activities [44]. Behavioral lifestyle variations and medical treatment enable heterogeneous results. The role of BoNT treatment has been emerging in the last decades. Recently, BoNT-B has been used to treat Raynaud's phenomenon and digital ulcers in 45 patients with systemic sclerosis. Patients were randomly divided into 4 groups: a control group receiving no treatment, and 3 treatment groups using increasing units of BoNT-B (250, 1,000 or 2,000 IU). The hand with more severe symptoms was treated. Results of this study

highlight the improvement in terms of both Raynaud's score (for 16 weeks after treatment) and the number of digital ulcers in patients treated with 1,000 and 2,000 IU of BoNT-B, as compared to the other 2 groups [45]. Furthermore, BoNT-A and B treatments have been proven to improve pulp temperature in patients with Raynaud, with or without systemic sclerosis [44,45].

Facial Flushing

Facial flushing consists of an episode of redness associated with a burning sensation. It can be primary or idiopathic and secondary to rosacea or hormonal stimuli like menopause. BoNT has been proven to provide symptomatic relief in patients with facial flushing through the inhibition of acetylcholine signaling pathway [46]. An open-label randomized controlled trial involving 24 patients with facial flushing showed an improvement within 2 to 3 weeks after the treatment. BoNT-A was injected, 1 IU per cm², for a total amount of 30 IU in one session [47]. However, other protocols have also been described. The injection of 100 IU of onabotulinumtoxinA diluted in 7 mL of saline solution, distributed in microdroplets (0.05 mL), has been reported to be effective [48].

A clinical trial involving 25 patients with facial erythema of erythematotelangiectatic rosacea was performed. The nasal tip, nasal bridge, and nasal ala of 15 patients completing the study were treated with abobotulinumtoxinA 15–45 IU. The assessment of clinical response followed a standardized grading system (0 = absent, 1 = mild erythema, 2 = moderate erythema, and 3 = severe erythema), revealing a significant improvement in erythema grade, as compared to baseline, at 1, 2, and 3 months after treatment ($P < .05$, $P < .001$, and $P < .05$, respectively) [49]. Although BoNT may cause headache, albeit rarely, it can be considered an option for reducing the severity of flushing [46,50]. However, studies with long-term follow-up are lacking [5].

Oily Skin

Oily skin is a common disorder, and treatment options often provide unsatisfactory results. The basis for BoNT-A treatment of oily skin, providing a reduction in sebum production, seems to lie in the expression of muscarinic acetylcholine receptors in sebaceous glands. These receptors control sebocyte differentiation and sebum production [3].

After preliminary data obtained on sebum reduction in a retrospective study, a prospective study involving 25 patients showing oily skin on the forehead was performed. Patients were treated with 10 intradermal injections of a total amount of 30–45 IU of abobotulinumtoxinA has been performed. A Sebometer (Courage + Khazaka Electronic GmbH, Cologne, Germany) was used to assess baseline and post-treatment

sebum production. All 23 patients completing the study were satisfied after the treatment, with variable degrees of satisfaction (21 were satisfied, 1 was very satisfied, and 1 somewhat satisfied). However, Sebumeter readings revealed a significant sebum reduction in all patients at 1 week and 1, 2, and 3 months ($P < 0.001$) [51]. Further studies are needed.

Psoriasis

The basis for BoNT-A use in psoriasis can be related to the inhibited release of substance P and CGRP. In particular, inverse psoriasis has been proven to benefit from BoNT, reducing both itch and pain. Intralesional BoNT-A has been employed for intertriginous psoriasis with the aim of reducing local sweating, skin maceration, and consequent infection. Subjective improvement of skin lesions was found in 87% of 15 patients injected with a total of 50100 IU of onabotulinumtoxinA per patient, depending on the extent and severity of lesions, with 2.4 IU per point and 2.8 cm apart [52].

No placebo-controlled studies are available at the moment, thus impairing a clear evaluation of the efficacy of BoNT in this disease [5].

Hailey-Hailey Disease

Similarly to what has been previously described for psoriasis, acanthosis and symptomatic relief seem to be the main effects of BoNT treatment in Hailey-Hailey disease. However, associated costs for achieving only temporary relief are a major issue [53]

Cutaneous Lesions

Pain relief has been evaluated in 18 patients with painful cutaneous leiomyomas who were randomized to obtain either onabotulinumtoxinA treatment versus placebo. BoNT-A was proven to be effective in pain improvement [54].

Periorbital syringomas are commonly treated with CO2 laser. However, the combined approach with onabotulinumtoxinA has been found to give better results in 48 patients, as compared to 44 subjects treated with CO2 only [55].

Conclusions

In conclusion, we describe innovative protocols and applications for BoNT use in dermatology, reviewing the literature of the last 5 years. Although the action of this drug has a complex mechanism, the effect of BoNT on many cellular types has been highlighted. Based on these data, several applications of BoNT have emerged. After the wide application for HH treatment, scars, as well as vascular and inflammatory skin disorders, oily skin and cutaneous lesions seem to be interesting fields of application of BoNT. On the other hand, there are

some factors limiting BoNT use, such as the high cost of the well-tolerated BoNT-A for chronic skin conditions.

Further studies are needed to improve the knowledge of the connection between BoNT and the cutaneous neuroimmune system and to better define standard protocols of treatment.

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