Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Utilities of Botulinum Toxins in Dermatology and Cosmetology

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Abstract: Botulinum toxin (BoNT) is a neurotoxin produced by the *Clostridium botulinum* bacterium with a well-known efficacy and safety profile in the focal idiopathic hyperhidrosis treatment. BoNT comprises seven different neurotoxins; however, only toxins A and B are clinically employed. BoNT is lately practiced in off-label therapies for a variety of skin diseases. Scar prevention, hyperhidrosis, rhytides, eccrine nevus, alopecia, psoriasis, Darier disease, bullous skin disease, pompholyx and Raynaud's phenomenon are some of the novel indications for BoNT in cosmetic and notably non-cosmetic aspects of dermatology. To employ BoNT correctly in clinical practice, we must have a thorough understanding of the functional anatomy of the mimetic muscles. An intensive literature search was conducted to update all dermatology-oriented experiments and clinical trials on the described element of BoNT for this general overview of BoNT use in dermatology. This review aims to analyse the role of BoNT in dermatology and cosmetology.

Keywords: botulinum toxin, BoNT, *Clostridium botulinum*, dermatology, cosmetology, neurotoxin

Introduction

Botulinum neurotoxin (BoNT) is produced naturally by *Clostridium botulinum*, an anaerobic, Gram-positive, spore-forming bacillus.[1] So far, seven serotypes of BoNT have been discovered (A to G), with only types A and B available for therapeutic usage. BoNT A (Oculinum) was approved by the Food and Drug Administration (FDA) in 1989 to treat blepharospasm and strabismus, the therapeutic value of BoNT A was first identified. The FDA did not authorize the use of BoNT A for the treatment of glabellar lines until April 2002. BoNT A was authorized by the FDA in October 2017 and September 2013 for the forehead lines and lateral canthal lines treatment, respectively. Several BoNT formulations have been introduced to the market since then.[2] BoNTs have been used for spasticity, depression, hyperhidrosis, migraines, and aging of the neck, face, and decolletage on and off label in the medical and cosmetic areas since their commercial availability.[3,4]

C. botulinum secretes a three-protein complex that includes a 150 kDa toxin, a non-toxic, non-haemagglutinin protein, and a non-toxic haemagglutinin protein. Bacterial proteases break the toxin into a di-chain active product with 50 kDa "light" and 100 kDa "heavy" chains. After already being transported to the presynaptic nerve terminal, the active toxin's heavy chain binds to synaptic vesicle glycoprotein 2, precipitating endocytosis of the toxin–glycoprotein complex and release of the toxin light chain into the synaptic space. Toxin light chains cleave vesicle-associated membrane protein/

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synaptobrevin (BoNT-B, D, F, G) or synaptosomal-associated protein 25 (BoNT-A, C, E), preventing acetylcholine release from peripheral motor neuron axons and resulting in transient chemical denervation and muscle paralysis.[2] In the United States, there are four commercially available, FDA-approved BoNT-A formulations: incobotulinumtoxinA (Frankfurt, Germany), onabotulinumtoxinA (California, USA), prabotulinumtoxinA-xvfs (California, USA) and abobotulinumtoxinA (Arizona, USA); as well as one BoNT-B: rimabotulinumtoxinB (California, USA).[5] A review by Guida et al[6] evaluated the role of BoNT in the field of dermatology. However, recently there are no reviews conducted on the application of BoNT in the field of dermatology and cosmetology. Therefore, the current review aims to analyse the role of BoNT in dermatology and cosmetology.

Methodology

With the specific keywords including botulinum toxin, oily skin, rosacea, facial flushing, scar, rhytides, alopecia, psoriasis, bullous skin disease, Darier Disease, eccrine nevus, pompholyx, Raynaud's phenomenon, hyperhidrosis adverse effects, dermatology and cosmetology, an article search was conducted in the following databases: Google Scholar, PubMed, MEDLINE, Scopus, and Cochrane. The author was mainly looking for articles on the role of BoNT in dermatology and cosmetology. The initial literature search revealed 3112 articles. Articles published between the years January 1990 and July 2021 with a description of BoNT in dermatology and cosmetology, articles published in the English language, and all study designs were included in this review.

Role of BoNT in Cosmetology

The use of BoNT for localized muscle spasticity and aesthetic treatment of wrinkles at the brow line was approved in Canada in 2000. The US FDA approved the use of BoNT for cosmetic purposes on April 15, 2002. Recent BoNT-A indications for cosmetics applications include glabellar frown lines, crow's feet, bunny lines, horizontal forehead lines, perioral lines, mental crease and dimpled chin, platysmal bands, mouth frown and horizontal neck lines.[7] The US FDA approved indications of onabotulinum type A are moderate-to-severe glabellar frown lines associated with procerus and/or corrugator muscle overactivity, moderate-to-severe lateral canthal lines associated with orbicularis muscle overactivity, and moderate-to-severe horizontal forehead lines associated with frontalis overactivity.[8]

BoNT in Oily Skin

Sebum helps supply fat-soluble antioxidants to the skin's surface and contains antibacterial properties; thus, it acts as a skin barrier. Excess sebum block pores feed germs and can cause skin inflammation (eg, seborrheic dermatitis, acne). Previously, relevant knowledge about the effect of BoNT on sebum production was revealed.[9,10] Rose and Goldberg[10] tested the efficacy and safety of BoNT on 25 people with oily skin. BoNT (abo-BNT, total dose of 30–45 IU) was injected into ten points on the forehead, resulting in significantly high patient satisfaction and reduced sebum production. Min et al randomly assigned 42 subjects with forehead wrinkles to receive 10 or 20 units of BoNT at five distinct injection locations. Both groups received BoNT treatment, which resulted in a considerable sebum decrease at the injection site, with a sebum gradient surrounding the injection point. At 16 weeks, both treatment groups' sebum production returned to normal levels, and efficacy did not improve significantly with greater injection doses.

The mechanism by which intradermal BoNT injection results in decreased sebum production is not entirely known because the influence of the nervous system and acetylcholine on sebaceous glands is not thoroughly described. BoNT's neuromodulatory effects are most likely to target the arrector pili muscles and local muscarinic receptors in the sebaceous glands. In vivo, the nicotinic acetylcholine receptor 7 (nAchR7) was expressed in human sebaceous glands, and acetylcholine signalling increased lipid synthesis in a dose-dependent manner in vitro.[11] More research is needed to determine who the most significant candidates are and the optimum injection procedures and doses (Figure 1A and B).

BoNT in Rosacea and Facial Flushing

Rosacea is a common inflammatory dermatosis marked by facial flushing, telangiectasia, papules, pustules, and erythema. Oral medicine, laser therapy, and topicals are routinely used to treat face flushing, although they do not always work. Another unpleasant menopausal symptom is facial flushing. Several studies have shown that BoNT can help with menopausal hot flashes and rosacea.[12–14] BoNT's impact on the Dermatology Life Quality Index (DLQI) of facial flushing patients was investigated in future pilot research.[15] BoNT was injected into the cheeks once, up to a total dose of 30 units, resulting in a significant decrease in DLQI at two months. BoNT significantly reduced the mean number of menopausal hot flashes at day 60, according to

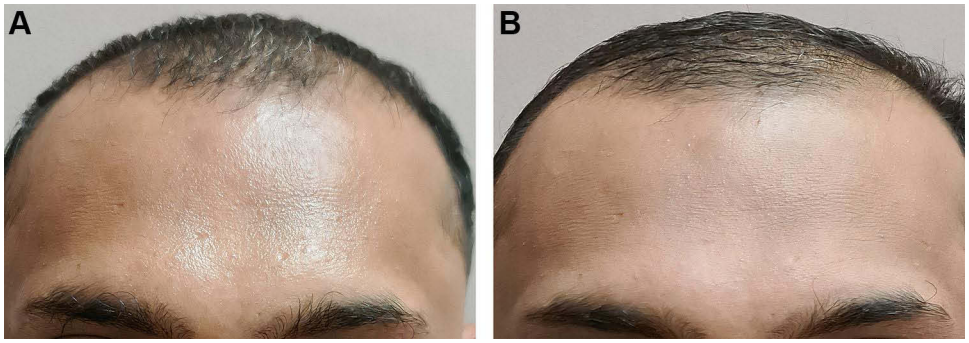

Figure 1 Upper image (A) of a patient with markedly oily skin, while on the opposite pole, inferior image (B) of the same patient after 2 sessions of BoNT shows significant improvement. (Technique: 100 units, 2.5 mL of intra-dermal BoNT-A was injected over forehead in one sitting. Total two similar sessions 30 days apart were administered. The good clinical response persisted for 6 months).

Odo et al.[12] The effects of abo-BoNT were also studied in 15 rosacea patients. 15–45 IU of BoNT was injected into the face three months later, resulting in a statistically significant erythema improvement.[13] In the studies, adverse effects were mentioned infrequently.

BoNT's flushing enhancement is one possible reason for its robust suppression of acetylcholine release from peripheral autonomic neurons of the cutaneous vasodilatory system.[16,17] Inflammatory mediators such as calcitonin gene-related peptide (CGRP) and substance P (SP) are also inhibited by BoNT, which is well-known.[18] The erythema may fade away if local skin inflammation is reduced and controlled. To assess the BoNT's role in rosacea, extensive, controlled, randomized studies are needed. BoNT injections for face flushing have additional advantages in that they reduce the pull of the facial depressors, which improves fine lines and wrinkles.

BoNT in Scar Prevention

Many people nowadays recognize the importance of active scar avoidance in postoperative scar treatment. The tension that acts on the wound edges during the healing process is a critical component that defines the final cosmetic look of a surgical scar.[19,20] BoNT provides for near-complete removal of dynamic muscular strain on the healing wound by preventing acetylcholine neurotransmitter release from peripheral nerves. BoNT's tension-relieving characteristics, as well as its direct inhibitory effects on fibroblasts and TGF-1 expression, suggest that it could be used to avoid surgical scars.[21–23] BoNT's anti-inflammatory effect and its effect on the cutaneous vasculature decrease the inflammatory phase of the wound healing process (from 2 to 5 days), which may help prevent scarring.

BoNT is useful in scar prevention in a variety of studies.[24–27] In an RCT, the safety and efficacy of early postoperative BoNT injection were assessed in 15 thyroidectomy scar patients.[24] Fresh scars (within ten days of thyroidectomy) were given a single dose of either BoNT (20–65 IU) or 0.9% saline (control), with the BoNT-treated halves demonstrating significantly superior scar scores and patient satisfaction than the saline-treated sides. Gassner et al[25] investigated if injecting BoNT into the face after forehead lacerations and excisions healed facial scars. Within 24 hours, BoNT (15–45 IU) was injected into post-op scars after wound closure to enhance cosmesis and wound healing, compared to a placebo (normal saline) injection.

Rhytides

Dynamic and static rhytides are formed by overactive musculature, photodamage, and aging, and patients perceive them as making them look tired or angry. Facial rhytides can be treated to offer people a more relaxed and refreshed appearance. The FDA currently has an exclusive authorization for BoNT for the treatment of periorbital and glabellar lines. BoNT is used off-label for the treatment of masseter hypertrophy, gummy smile, platysmal bands of the neck, mandibular border, dimpled chin, horizontal forehead lines, downturned smile, perioral lines, horizontal nasal lines and ptotic brow and with clinical results lasting about three months[28,29] (Figure 2A and B).

Psychological Improvement

BoNT enhances patient mood and perceived confidence when used in conjunction with rhytide decrease. Improvements in the FACE-Q score have been observed after treatment of moderate-to-severe glabellar lines. Even after 120 days, when the clinical effects of BoNT should be

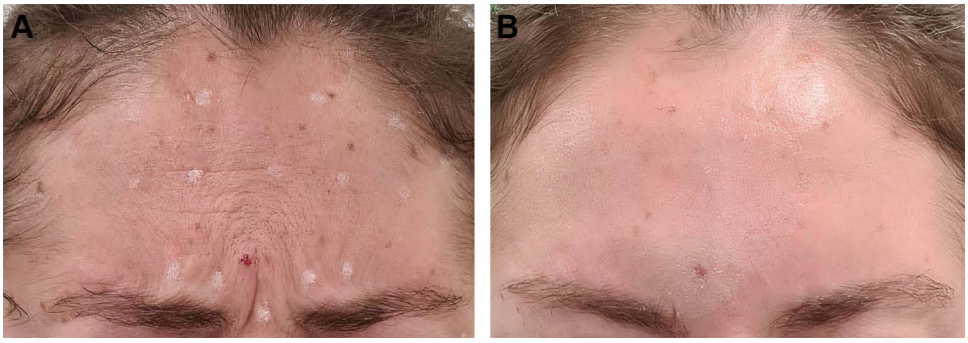

Figure 2 Pre-botox superior image (A) of a case shows horizontal forehead lines and glabellar lines giving the subject angry look, on the other hand, inferior image (B) of the same case after two sessions of botox clears away those lines with ease. (Technique: 36 units, 0.9 mL of intra-dermal BoNT-A was injected over forehead in one sitting. Skin pencil was used to mark the injection sites prior to therapy. Total two similar sessions were given 30 days apart).

diminishing, patients have reported improved psychological well-being and improved facial attractiveness.

Instead of automatically reinjecting BoNT every three months to have the best clinical and psychological response, practitioners should talk to patients about when retreatment is essential.[30,31] Furthermore, BoNTs have been used successfully to prevent and treat migraines in neurology, with an improvement in patient quality of life and well-being[32] (Figure 3A and B).

The FDA-approved commercially available BoNT is listed in Table 1.

Role of BoNT in Dermatology

Alopecia

Alopecia areata, androgenetic alopecia, cephalalgic alopecia and radiation-induced alopecia have all been treated with BoNT-A. Although the exact mechanism by which BoNT helps hair regrowth is uncertain, it is assumed that by decreasing microvascular pressure by relaxing muscles, oxygen supply to hair follicles may be improved. Throughout 1–12 sessions, 30–150 U is injected into the frontal, periauricular, temporal and occipital muscles (Figure 4A and B).

Although most studies show a clinical improvement in density or growth of hair and high patient satisfaction, further RCTs are needed to determine the actual effect of BoNT on hair growth.[33–35] Multiple BoNT injections for forehead wrinkles, on the other hand, have been linked to the onset of frontal alopecia.[36]

Psoriasis

Several studies have suggested that the neurological system plays a role in psoriasis, with high nerve fiber concentration in psoriatic skin and higher sensory nerve derived CGRP and SP levels. As a result, clinical evidence indicating that psoriasis remits following the loss of innervation are growing, nervous system injury or nerve function supports this hypothesis.[37] BoNT-A reduces nerve-derived CGRP and

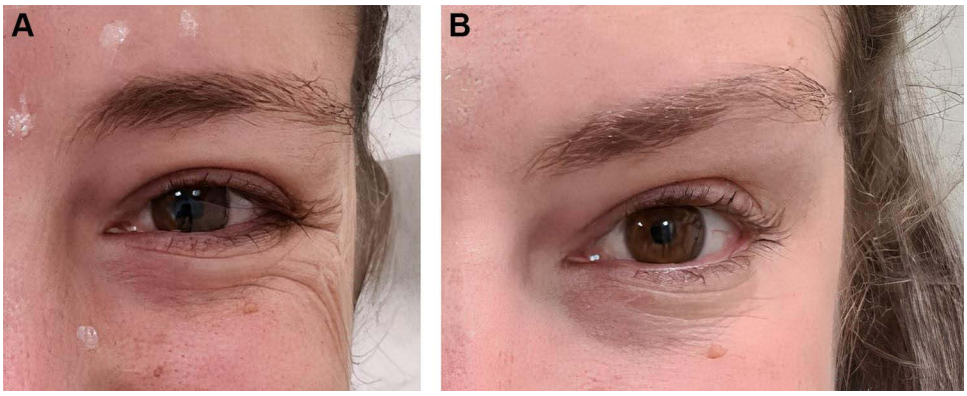

Figure 3 Superior image (A) of a subject shows lateral periorbital lines giving aged and tired look, on the other hand, inferior image (B) of the same case after a session of botox eliminates those lines and elevates the lateral eyebrow to give glance. This subject also expressed enriched emotional health succeeding this sitting. (Technique: 16 units, 0.4 mL of intra-dermal BoNT-A was injected per lateral periorbital region in one sitting. Only one session culminated in dramatic response which persisted for 4 months).

Table 1 Commercially Available BoNT and Its Characteristics

Commercially Available Toxin & Serotype	FDA Approval	Molecular Weight (kDa); Units per Vial
PrabotulinumtoxinA-xvfs (PRA; JeuveauTH) & A	Cosmetic: glabellar lines	900;100
IncobotulinumtoxinA (INCO; Xeomin ®) & A	Medical: blepharospasm, cervical dystonia. Cosmetic: glabellar lines.	150; 100
OnabotulinumtoxinA (ONA; Botox*) & A	Medical: axillary hyperhidrosis, blepharospasm, migraine, strabismus, Cosmetic: glabellar lines, periocular rhytides	900; 100
AbobotulinumtoxinA (ABO; Dysport ®) & A	Medical: blepharospasm, cervical dystonia. Cosmetic: glabellar lines.	300–500; 500
Rimabotulinumtoxin (RIMA; Myobloc ®) & B	Medical: cervical dystonia	700; 5000

SP release, which may explain the subjective clinical observation of disease improvement in inverse psoriasis after treatment with the drug.[38] In adult KC-Tie2 mice, intradermal injections of BoNT-A resulted in a considerable reduction in cutaneous lymphocyte infiltration and a significant acanthosis improvement compared to placebo.[37] However, there are few published clinical reports and observational studies, and none of them is placebo controlled. In 15 inverse psoriasis patients, Zanchi et al[38] reported a favorable response to the BoNT-A treatment; however, the outcomes were assessed using patient self-assessment and an infiltration photographic evaluation and erythema. As a result, Chroni et al[39] noted various concerns about the study, including the lack of a quantitative metric to estimate improvement (such as a PA score). The authors postulated that BoNT-A has a favorable effect in lowering local sweating in folds, such as Hailey-Hailey disease, where the efficacy of BoNT-A is due to sweating decrease.[40–42] The capacity of BoNT-A to prevent algogenic neuropeptide liberation, however, resulted in a reduction in pain and itch for the patients.[43]

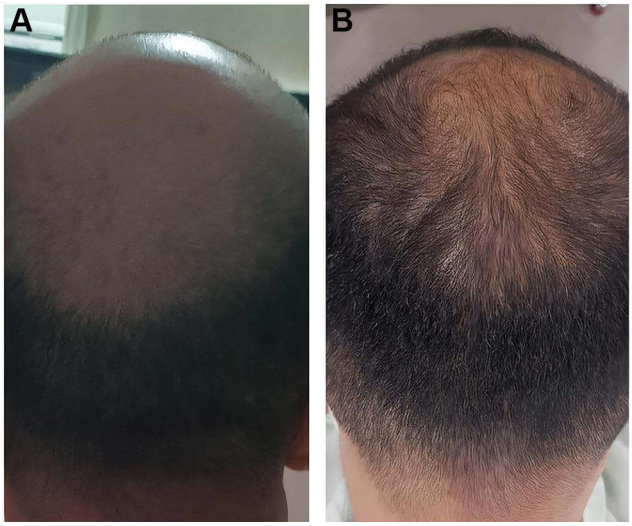

Figure 4 Left half of clinical photograph (A) shows type 6 male-pattern hair loss according to adopted Norwood-Hamilton classification in a 34-year-old male. In contrast, same patient after 12 sessions of botox showed down-grading to type 3V on culmination (B). (Technique: 100 units, 2.5 mL of intra-dermal BoNT-A was injected in top of the head region in one sitting. Total 12 similar sessions 15 days apart resulted in acceptable clinical response which persisted for 4 months).

Bullous Skin Disease

Off-label, BoNT has been used to treat a variety of bullous skin diseases such as linear IgA bullous dermatosis, Weber–Cockayne disease and Hailey-Hailey disease. BoNT-A injections, oral tacrolimus, yttrium aluminum garnet ablative laser, BoNT-A with erbium have been used to treat Hailey-Hailey disease in the inframammary, axillae, groin, and intergluteal cleft regions. After treatment, there is improvement in clinical signs, with doses ranging from 25 to 200 U every 3 to 6 months.[42,44] In the case of reports, a middle-aged female with regional epidermolysis bullosa simplex had 50 U per axilla injected into her foot, and 100 U was injected into the foot of a young patient with linear IgA bullous dermatosis.[45,46]

Darier Disease

The first use of BoNT-A as adjuvant therapy in Darier illness was reported in 2007 when Kontochristopoulos et al[47] effectively treated a 59-year-old patient's submammary regions. In another case from 2008, sweating decrease in the intertriginous area was beneficial in a young child with severe

anogenital involvement.[48] Her concomitant infection was treated with acitretin 10 mg per day and antibiotic and antifungal medicines, but her low quality of life and discomfort persisted. Both symptoms and clinical lesions improved significantly after three weeks of BoNT-A injections.

Eccrine Nevus

Eccrine nevus is a rare cutaneous hamartoma characterized by an increase in the number of eccrine glands but no vascular development. The eccrine nevus differs from other disorders like angiomatous eccrine hamartoma because of this last feature.[49] Eccrine nevus is most commonly found on the forearms, with minimal skin problems but a localized hyperhidrosis area.[50] Surgical excision or topical medications are the most popular treatments, depending on the size covered and the hyperhidrosis entity. Honeyman et al[51] documented a 12-year-old child with a congenital eccrine nevus of the right wrist resistant to topical antiperspirants. Due to the magnitude of the tumor and its anatomical position, surgical excision was ruled out. Hyperhidrosis makes it challenging to participate in social and intellectual activities. The researchers chose to inject 5 U of BoNT-A at 0.5–1 cm interval. The authors did not say when the first reaction to BoNT-A treatment occurred, but they did say that a year later, they noticed a considerable sweat episode reduction to once a month and the quality of life of the patients was increased. Lera et al[49] treated an eccrine nevus patient on the forearm who had a low quality of life and an HDSS score of 3 on the hyperhidrosis disease severity scale (HDSS) (severe). BoNT-A (100 IU) was reconstituted in a 2.5 mL sterile saline solution containing 0.9% sodium chloride and given into the minor iodine test area. After 48 hours, the patient noticed a decrease in sweating, with the best outcomes at week three. The HDDS score fell to one. Because of relapse in sweating, the BoNT-A treatment was repeated after nine months. In the treatment of eccrine angiomatous hamartoma, an injections therapy of BoNT-A is useful.[52] Despite the condition's rarity, it is simple to see how critical it is for these people to have a viable therapy option.

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic skin disease characterized by painful, scarring, sinus tracts, fistulas, inflamed nodules and deep-seated in apocrine gland-bearing parts of the body in the latter stages.[53] The pathophysiology of the condition is still unknown, and previously accepted hypotheses of HS development are now being challenged. The occlusion of the hair follicle is crucial in the symptoms of HS, although the mechanism that causes occlusion is unknown. Skin lesions develop in HS as a result of subsequent inflammation and a combination of innate and adaptive immunological dysfunction.[54] A study by Feito-Rodriguez et al[55] reported that the BoNT-A was successfully treated the prepubertal HS in 6-year-old girl. A case report by Shi et al[56] observed that the BoNT-A was successfully treated the stage −3 HS in 41-year-old female. Recently, a study by Grimstad et al[57] assessed whether intradermal injection with BoNT-B is an effective treatment for HS among 20 patients. The DLQI in the BoNT-B group improved from a median of 17 at baseline to 8 at 3 months, compared to a decrease from 13.5 to 11 in the placebo group.

Notalgia Paresthetica

Notalgia paresthetica (NP) is a persistent sensory neuropathy affecting the interscapular area, particularly the T2-T6 dermatomes, with itching on the upper back and cutaneous symptoms linked with rubbing and scratching. BoNT-A may help with localised pruritus by blocking the release of substance P, a pain and itch mediator.[58] A case report by Weinfeld[59] evaluated the efficacy of BoNT-A among two cases. Both are successfully treated with the BoNT-A. A study by Perez-Perez et al[58] assesses efficacy of BoNT-A among five patients diagnosed with NP. After the delivery of intradermal BoNT, a variety of effects were seen. There was no complete relief of the pruritus in any of the individuals. A randomized controlled trial (RCT) by Maari et al[60] evaluated the efficacy and safety of BoNT-A in patients with NP in a Canadian dermatology research clinic between July 2010 and November 2011. This study was not able to confirm the beneficial effect of BoNT-A injected intradermally at doses of at most 200 U to reduce pruritus in patients with NP.

Pompholyx

Pompholyx, also known as dyshidrotic eczema, is a recurrent vesicular-bullous illness that affects the palms and soles. Although the pathophysiology of this condition is unknown, it is now thought to be a symptom of atopic dermatitis.[61] Wet works, sweating, and occlusion are the most common inciting elements.[62] Wearing gloves or shoes causes pain, burning, itching, and discomfort in patients; bacterial infections are prevalent. Swartling et al[61] found that patients treated with BoNT-A for palmar hyperhidrosis improved their hand eczema. In 2002, they presented the results of a study involving ten individuals with bilateral vesicular hand dermatitis; one hand was treated with BoNT-A injections, while the other hand served as a control at the follow-up. The treatment had a good or excellent effect on 7 out of 10 patients. In

six patients, Wollina and Karamfilov[63] employed topical corticosteroids on both hands and intracutaneous injections of 100 U of BoNT-A on the most severely affected hand. In hand treated with combination therapy, the authors discovered a quick reduction in itching and vesiculation, and they attributed BoNT-A efficacy in pompholyx to its anhidrotic action as well as its suppression of SP.

Raynaud's Phenomenon

Vasospasm of the digits, also known as Raynaud's syndrome, is challenging to treat and often resistant to first-line medications such as bosentan, iloprost, phosphodiesterase inhibitors, nitrates, and calcium channel blockers. Surgical procedures that involve recovery and downtime, such as sympathectomy, are invasive. Raynaud's phenomenon of the fingers, both primary and sclerosis-related, has been successfully treated with BoNT injection.[64,65] Investigators noticed that 13 patients experienced rapid pain relief, and chronic ulcers healed within 60 days after receiving 50–100 U of BoNT-A injections in 19 Raynaud's phenomenon patients.[66] After six weeks, digital pulp temperature in the fingertips treated with BoNT dramatically improved compared to normal saline injections, indicating that BoNT is beneficial in treating Raynaud's phenomenon-associated vasospasm.[67] For the time being, there are no standardized injection procedures in use; injections in the digits, wrist or distal metacarpus did not result in significantly different clinical outcomes, according to one study, despite the fact that they were all effective in treating Raynaud's phenomenon-associated vasospasm.[68]

Hyperhidrosis

50–100 U of BoNT-A per axilla, administered intradermally in a grid-like design, can be used to treat primary axillary hyperhidrosis. Clinical outcomes are visible within one week and last for 3 to 10 months. Most patients are satisfied with their treatment. Patients should be advised that compensatory sweating can occur in up to 5% of cases.[69,70] BoNT is also effective for treating palmar and plantar hyperhidrosis (Figure 5A and B).

With 2–3 injection locations per digit, injections should be placed 1 cm apart in a grid-like arrangement. BoNT-A can be given to each hand in the range of 75–100 units and to each foot in 100–200 units. Clinical results can take up to a week to manifest and can last for three to six months. Patients should be informed about the potential side effects of BoNT injections in their palms and feet before starting treatment. Patients may report weakness after a palmar injection. On the other hand, plantar injections may make walking difficult, especially if a nerve block is done before BoNT treatment.[71,72] Unfortunately, 20% of patients with plantar hyperhidrosis who get BoNT injections do not react to treatment.[72]

BoNT has been used to treat hyperhidrosis in new ways in recent research. In one case, a male patient with pressure-induced ulceration received 100 U of BoNT-A injected into the gluteal cleft every 6–8 months to reduce sweat production and concomitant wound maceration; skin integrity was preserved over two years with no clinical deterioration of the pressure injury.[73] Another study used 2250 U of BoNT-B injected in a band-like pattern across the occipital scalp, parietal scalp, frontal scalp, and forehead, as well as perioral and periocular areas, to treat postmenopausal craniofacial hyperhidrosis. Patients who received BoNT-B had a 91% improvement in the DLQI three weeks following therapy, compared to an 18% decline in quality of life with placebo injections.[74] In treating sialorrhoea and Frey's syndrome, the BoNT injection is effective. Otolaryngologists frequently conduct treatment due to the anatomic position of injections.[75,76]

Chromhidrosis and Bromhidrosis

Pigmented sweat could be markedly unsettling condition for patients. Though this disorder is quite rare; facial and axillary involvement can add to patient's plight. Numerous

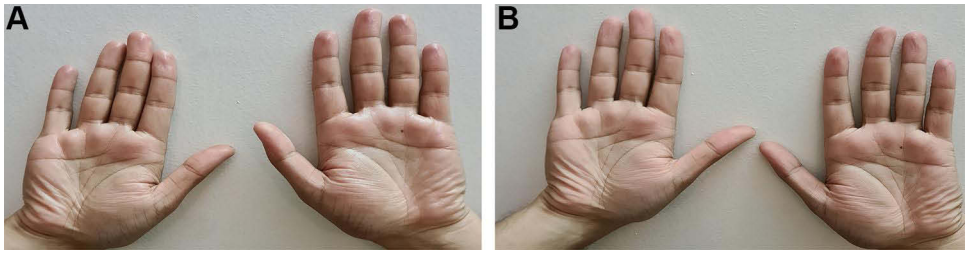

Figure 5 Superior clinical image (A) shows diffuse palmar hyperhidrosis in a young college student feeling anxious about the disorder and not responding to medical treatment. Similar patient after a botox therapy demonstrated complete resolution of hyperhidrosis (B). (Technique: After confirmation with starch iodine test; 100 units, 2.5 mL of intra-dermal BoNT-A was injected per hand in one sitting. Total two similar sessions 15 days apart resulted in dramatic response which persisted for 6 months).

case reports and publications have demonstrated positive outcome after BoNT-A injections within just seven days.[77–79]

Obnoxious smell from axillary hyperhidrosis, bromhidrosis could be embarrassing as well socially repellent. This could even have negative impact on mental space and confidence of the patient. Recently, Wu et al reported near complete elimination of bad smell from axilla after intracutaneous BoNT-A injections.[80] In another contemporary, prospective study; 62 adolescents with dermatological diagnosis of primary axillary bromhidrosis were enrolled. 82.25% patients perceived notable abatement of malodour when their axillary regions were subjected with BoNT-A injections.[81]

Multiple Eccrine Hidrocystomas (Meh)

Meh is identified by single or multiple benign cystic lesions in middle-aged females, predominantly in centrofacial region with protracted course and seasonal fluctuations. Meh is usually seen in sunny conditions and linked with hyperhidrosis. Many researchers have observed exceptional results in these cases after perilesional injections of BoNT-A.[82]

Post-Herpetic Neuralgia

Post-herpetic neuralgia (PHN) is the most frequent neurological complication of Herpes Zoster infection, which is more common in more than 60 years of age. BoNT-A imparts its pan inhibition directly on the local nerve ending as well as through modulation of microglial-astrocytic-neuronal crosstalk. Numerous studies noticed remarkable attrition in sleep scores and quality of life in those patients with at least 30% to 50% decrement in pain on treating with BoNT-A.[83]

Lichen Simplex Chronicus

Lichen simplex chronicus is described as excessive focal itching without any obvious reason. This can be enormously debilitating to patient. Clinical dermatological examination shows lone erythematous patch with increased skin markings and excoriations. Recent landmark study from Egypt demonstrated that BoNT-A can be safe and effective treatment in localized recalcitrant pruritus of lichen simplex chronicus, hypertrophic lichen planus, lichen planus, burns, inverse psoriasis, and post-herpetic neuralgia.[84]

Keloids

Keloids are aberrant tissue scarring occurring after the injury. Keloids have genetic association and many therapies have been tried on them with limited success. However, none of them is completely curative. Although intralesional corticosteroids remain the main stay of treatment, intralesional BoNT-A have become an excellent alternative in recent days. BoNT-A can reduce the levels of TGF-β1 and CTGF, which will ultimately attenuate fibroblast differentiation. Multiple studies have demonstrated therapeutic success of BoNT-A in keloid cases. In fact, two case series of keloid patients even reported 100% response with very high patient satisfaction with the use intralesional BoNT-A injections.[85]

Pachyonychia Congenita

Pachyonychia congenita is a rare genetic disease with hyperkeratosis of soles, hypertrophy of nails and hyperhidrosis. Few researchers have concluded that BoNT-A injections not only improve hyperhidrosis, but it can also lead to reduction in pain and discomfort.[86,87]

Aquagenic Keratoderma

Aquagenic keratoderma is an uncommon condition in which patients suffer from thickened, white pebbly of soles and palms on exposure to water along with itching. Several case reports in literature showed successful treatment and improvement after BoNT-A therapy, also in resistant cases.[88]

Adverse Effects and Complications Associated with the BoNT

Bleeding, edema, erythema, and pain at the injection sites are all possible BoNT adverse effects.[89] By using thinner needles and diluting BoNT with saline, these side effects can be prevented. BoNT injections can cause headaches; however, they usually go away after 2–4 weeks. Systemic analgesics can be used to address this side effect.[90,91] Nausea, malaise, influenza-like symptoms, and ptosis are some of the other side effects that have been recorded.[89] Ptosis is a side effect of using BoNT to treat the glabellar area. It is produced by localized BoNT diffusion, which might last for weeks but can be addressed with alpha-adrenergic agonist ophthalmic drops. When BoNT is injected into the lower eyelids, it can cause ectropion due to the local diffusion process. In addition, patients who receive BoNT injections to cure crow's feet or bunny lines (periorbital) may develop strabismus as

a result of inadvertent injection of BoNT and localized BoNT diffusion.[89,92] Nonetheless, as the toxin's paralyzing effect wears off, all of these side effects will fade away.[93,94]

Cosmetic BoNT injections have a low risk of complications. Ecchymosis and purpura are the most prevalent consequences, which can be reduced by applying cold to the injection sites before and after the BoNT injection.[90,91] BoNT should be injected in low doses, at least 1 cm from the inferior, superior, or lateral margins of the orbital bone, with the appropriate dose. Patients should not manipulate the injected areas for 2–3 hours after therapy and sit or stand upright for 3–4 hours after treatment.[95]

Future Direction

BoNT-A in various novel formulations is currently being tested to treat glabellar and periocular lines. Topical and injectable daxibotulinumtoxinA has been investigated, but the topical formulation was shown to be ineffective. Injectable DAXI has entered FDA Phase III trials, demonstrating efficacy in the treatment of glabellar lines and clinical outcomes that could last up to 5 weeks longer than onabotulinumtoxinA.[96] LetibotulinumtoxinA is now available in Asia and studied for FDA approval to treat periorbital rhytides.[97] LetibotulinumtoxinA has a more significant concentration of neurotoxic protein per volume than incobotulinumtoxinA, but it also has a higher quantity of inactive neurotoxin, increasing the immunoreaction risk.[98]

Liquid BoNT-E is being studied in addition to novel BoNT-A formulations because of its purportedly faster onset of action and shorter clinical results duration (14–30 days). EB-001 has been found to decrease the appearance of the glabellar lines safely and effectively and improve the cosmesis of forehead scars following Mohs micrographic surgery.[99] Dermatologists may be permitted to use these books. Pharmaceutical companies are pursuing BoNT-A formulations for off-label therapy of dermatologic medical conditions in addition to the current aesthetic purposes.

Conclusion

BoNT is a highly adaptable injectable medicine that can be used to treat a wide range of skin disorders, including Hidradenitis suppurativa, psoriasis, bullous skin disorders, abnormal scarring, hair loss, and hyperhidrosis and keloids. In cosmetic applications, BoNT is considered safe and effective for reduction of facial wrinkles, especially in the uppermost third of the face. BoNT A is well known for its use in the cosmetic world to reduce wrinkles. Although BoNT is usually safe, it is always vital to be aware of injection places because the toxin might disperse and negatively affect areas that should not have been treated. Clinicians should be aware of site-specific complications when injecting BoNT into the feet, hands, or neck. Dermatologists need to be acquainted with both the on- and off-label uses of BoNT to provide patients with pertinent treatment and decrease associated morbidity. BoNT's clinical efficacy in an off-label setting, as well as any potential long-term safety concerns, should be assessed by well-designed clinical trials.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Compliance with Ethics Guidelines

The examination of the patients was conducted according to the principles of the Declaration of Helsinki. The author certifies that she has obtained all appropriate patient consent forms, in which the patients gave their consent for images and other clinical information to be included in the journal. Patients understand that their names and initials will not be published, and due effort will be made to conceal their identity.

Author Contributions

Dr. Piyu Parth Naik solely contributed to manuscript writing. The author made substantial contributions to conception and design, acquisition of data, and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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