



Review

Botulinum toxin: Non cosmetic and off-label dermatological uses

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Received 23 April 2014; accepted 12 June 2014

Available online 18 September 2014

Abstract

Botulinum toxin (BT-A) is a neurotoxin which is produced by the Gram-positive anaerobic bacterium *Clostridium botulinum*. The efficacy of Botulinum toxin in treating hyperhidrosis and the glabellar lines is well known and FDA approved.

Because BT-A inhibits the release of acetylcholine and many other neurotransmitters such as norepinephrine and substance P at the level of nerve ending, this toxin has been used to treat a lot of dermatological disorders which are thought to be triggered by these neurotransmitters.

In this article we are discussing the medical off-label uses of BT-A in dermatology.

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Keywords: Botulinum toxin; Hyperhidrosis; Hailey-Hailey; Post-herpetic Neuralgia; Leiomyoma-related pain; Lichen simplex chronicus; Raynaud Syndrome

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Peer review under responsibility of King Saud University.



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1. Introduction

Botulinum toxin (BT-A) is a neurotoxin which is produced by the Gram-positive anaerobic bacteria *Clostridium botulinum*. *C. botulinum* bacteria produce neurotoxins which cause Botulism; a disease that is characterized by potentially life-threatening neuroparalysis.

There are seven distinct serotypes of Botulinum toxin : A, B, C1, D, E, F, and G. Human botulism is caused mainly by types A, B, E, and (rarely) F [Aoki, 2001](#).

C. botulinum bacterium was first identified in 1895 and was isolated in the 1920s. In 1989 Food and Drug Administration (FDA) approved the use of Botulinum toxin (BOTOX[®]) for treatment of strabismus and blepharospasm.

In 2002 was the first dermatological and Cosmetic FDA approval of Botulinum toxin (BOTOX[®]) for moderate to severe glabellar lines. And in 2004 it was approved for axillary hyperhidrosis.

2. Types of Botulinum toxin

As we said , there are 7 serotypes of Botulinum toxin A, B, C1, D, E, F, and G , but the commercially available Botulinum toxins are only from type A – mainly – and type B.

The most widely used Botulinum toxins commercially are:

1. Onabotulinumtoxin A (Botox[®])
2. Abobotulinumtoxin A (Dysport[®])
3. Incobotulinumtoxin A (Xeomin[®])
4. Rimabotulinumtoxin B (Myobloc[®])

3. Mechanism of action of Botulinum toxin

Botulinum toxin is a single-chain protein that is inactive until cleaved by its own proteases into one heavy and one light chain. Once the toxin enters the nerves by binding to surface protein receptors or endocytosis into internalized vesicles ([Eric, 2006](#)).

The light chain is released into the nerve cytosol, and the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) protein complex is cleaved

to inhibit exocytosis of the neurotransmitters such as acetylcholine.

Type A toxin cleaves SNAP-25 (synaptosome-associated protein of 25 KDa), whereas type B cleaves VAMP (vesicle-associated membrane protein).

These proteins are necessary for the release of acetylcholine from vesicles within the cytoplasm of the motor nerve endings [Fig. 1](#).

The end results are chemoprevention of cholinergic neurons which lead to temporary paralysis of the targeted skeletal muscles, decreased sweating or decrease in the pain at the site of injection.

3.1. Non dermatological uses

The first FDA approval of Botulinum toxin was in 1989 for strabismus and blepharospasm which are non-dermatologic conditions, since that time many medical and surgical specialties have tried Botulinum toxin in a lot of specific conditions in their fields, the non dermatological indications of BT-A are listed in [Table 1](#).

3.2. Dermatological uses

The first FDA approval for Botulinum toxin in dermatology and dermatological surgery was in 2002 for Cosmetic treatment of moderate to severe glabellar lines, and in 2004 it was approved to treat severe primary axillary hyperhidrosis ([Teo et al., 2012](#); [Ney et al., 2007](#)).

Based on the mechanism of action that has been discussed above, Botulinum toxin has been tested in many skin conditions in a lot of case reports and case series , but the use of Botulinum toxin in all of these disorders is still off-label.

We can divide the skin diseases in which Botulinum toxin was tested as one of the treatment options into two groups ([Table 2](#)).

1. Sweating related disorders.
2. Pain and itchiness related disorders.

These off-label disorders will be discussed in this article, but the discussion of the cosmetic and FDA approved conditions is beyond the scope of this article.

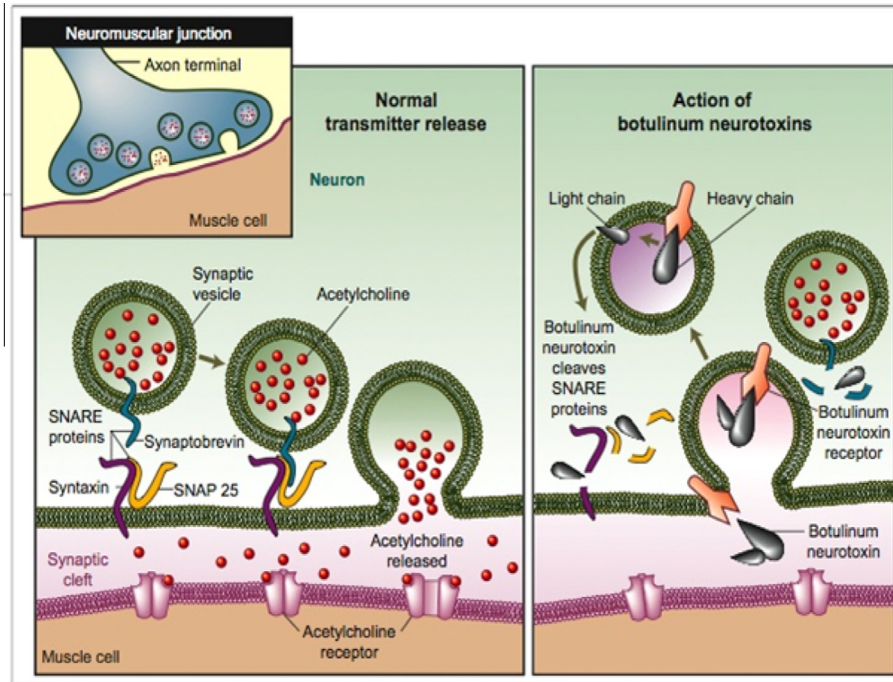


Figure 1. Mechanism of action of Botulinum toxin. The light chain of (BT- A) cleaves SNAP-25 and consequently prevents the release of ACh into the neuromuscular junction.

Table 1
Non dermatological uses of Botulinum toxin.

Ophthalmology	Neurology	Urology and Gynaecology	Gastrointestinal
<ul style="list-style-type: none"> • Blepharospasm • Reduce lid retraction • Apraxia of lid opening • Exposure keratopathy • Lower lid spastic entropion • Infantile esotropia • Intermittent exotropia • Nerve palsies • Congenital nystagmus • Lacrimal hypersecretion • Pain relief in acute angle closure glaucoma 	<ul style="list-style-type: none"> • Hemifacial spasm • Facial asymmetry • Oromandibular dystonia • Cervical dystonia • Spasmodic torticollis • Achalasia • Gustatory sweating • Synkinesia • Headache 	<ul style="list-style-type: none"> • Detrusor overactivity • Detrusor sphincter dyssnergia • Bladder overactivity • Painful bladder syndrome • Pelvic pain • Outflow obstruction symptoms • Urinary retention 	<ul style="list-style-type: none"> • Achalasia • Anal fissure • Biliary dyskinesia

Table 2
Dermatological uses.

FDA approved use of Botulinum toxin

- Axillary hyperhidrosis
- Glabellar lines

Dermatological uses

Off-label uses

Sweating related disorders

1. Hailey-Hailey
2. Dyshidrotic hand eczema (pompholyx)
3. Granulosis rubra nasi
4. Pitted keratolysis
5. Chromhidrosis
6. Inverse Psoriasis
7. Eccrine hydrocystomas
8. Eccrine Angiomatous Hamartoma
9. Aquagenic syringeal acrokeratoderma

Pain and itchiness related disorders

- Post-herpetic Neuralgia
- Leiomyoma-related pain
- Lichen simplex chronicus
- Raynaud Syndrome
- Notalgia Paresthetica
- Thelalgia
- Brachioradial pruritus
- Vulvodynia

3.3. Sweating related disorders

3.3.1. Hailey-Hailey disease

Hailey-Hailey disease or familial benign pemphigus is a chronic autosomal dominant disorder in which there is loss-of-function and mutations in the ATP2C1 gene. The skin lesions in this chronic disorder are frequently induced or exacerbated by UV exposure, sweating, friction, and skin infection.

Many topical and systemic therapies have been proposed with limited success.

Because Hailey-Hailey disease is induced by excess sweating Botulinum toxin type A has been evaluated to treat Hailey-Hailey disease in many case reports, In 6 patients with extensive Hailey-Hailey disease resistant to multiple therapeutic regimens; Abobotulinumtoxin A was started in all six cases as adjuvant treatment and there was a marked improvement achieved of the lesions with few side effects in all patients (Smith et al., 2004).

In another study 3 patients with axillary and/or inguinal benign familial pemphigus responded favorably to treatment with subcutaneous botulinum toxin type A (Onabotulinumtoxin A) (Qureshi, 2002) Fig. 2.

Many additional case reports showed the same beneficial effect of Botulinum toxin as one of the treatment options for Hailey-Hailey disease (Grunfeld, 2009; Doft, 2012; Koeyers et al., 2008; López-Ferrer, 2012).

3.3.2. Multiple eccrine hidrocystomas

Eccrine hidrocystoma is a benign cystic lesion which can be either solitary (Smith type) or multiple (Robinson type). Multiple eccrine hidrocystomas are characterized by chronic course and seasonal variability in which it is associated with warm climates and hyperhidrosis. It occurs mainly in middle-aged women in the centrofacial area.

The efficacy of Botulinum toxin type A was evaluated in many reports of multiple facial hidrocystomas with excellent outcome (Bessa et al., 2010; Pérez-Robayna, 2010; Lapiere et al., 2000; Konrad et al., 2001).

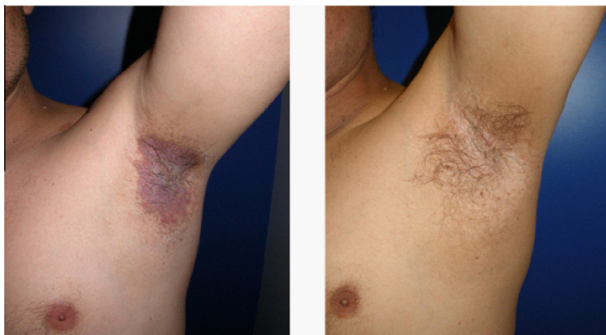


Figure 2. Erythematous–violaceous plaques and erosions in the axilla in a patient with Hailey-Hailey disease before treatment and clinical resolution of the erosions after injection of Botulinum toxin. Photograph courtesy of Dr. A. López-Ferrer Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

In one study on 22 patients (16 F and 6 M) with eccrine hidrocystoma documented pathologically and the patients were divided into two groups, with 12 pts in the and 10 pts in the 2nd group. BT-A (Abobotulinumtoxin A) was injected perilesionally and intradermally at a concentration of 5 and 10 units in 0.01 ml respectively.

There was excellent response at first session in around 80% of both groups with mean duration of 7 months of the drug efficacy (Correia et al., 2009).

In another case report of two female patients with multiple facial eccrine hidrocystomas, both of them were injected with BTX-A (Onabotulinumtoxin A) with excellent results within one week of injection and the efficacy duration was 6 months in both patients (Blugerman, 2003) Fig. 3.

3.3.3. Dyshidrotic eczema (Pompholyx)

Pompholyx or Dyshidrotic Eczema (DE) is a relapsing vesicular eruption on the hands or feet, most often without erythema. The acrosyngium is not involved in the pathogenesis of pompholyx, but hyperhidrosis is an aggravating factor in nearly 40% of these cases.

Botulinum toxin had been used for the treatment of pompholyx in many studies, ten patients with pompholyx were treated on one hand with intradermal BT-A (mean, 162 U Onabotulinumtoxin) with the untreated hand as a control. At follow-up 5 to 6 weeks after injection showed that 7 of 10 patients experienced good or very good effect (Ebrahimi, 2010).

It was shown that BT-A was effective as an adjuvant treatment not as single agent; 8 patients were treated with topical steroids in both hands and BT-A injection in the more affected hand.

The mean DASI score (Dyshidrotic Eczema Area and Severity Index) changed from 28 to 17 with topical therapy alone and from 36 to 3 with adjuvant BT-A. Also itching and vesiculation were inhibited and relapses have not been seen in the BT-A group (Woolery-Lloyd, 2009).

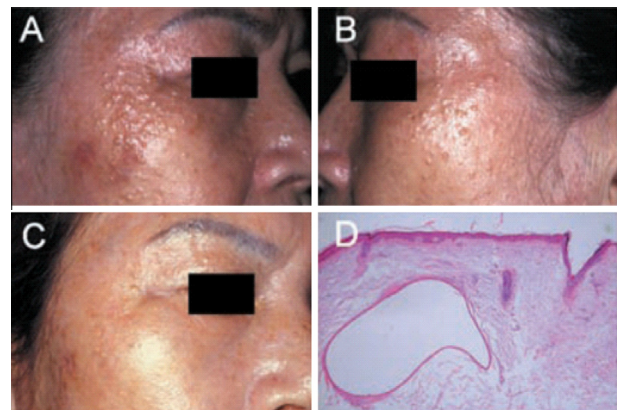


Figure 3. (A and B) Multiple, dome-shaped, bluish to skin-colored papules, over the periorbital areas and bilateral cheeks. (C) Significant lesional fading was achieved 7 days after injection. (Photograph courtesy of Dr. Ta-Ju Liu Chang Gung University, College of Medicine, Kaohsiung, Taiwan with permission).

3.3.4. Chromhidrosis

Chromhidrosis is a rare disorder characterized by the excretion of pigmented sweat. It is frequently confined to the face or axillae. The colored sweat may be yellow, blue, green, or black. There is a debate wither the origin of the sweating in chromhidrosis is eccrine or apocrine, but most likely it originates from the apocrine gland due to the presence of lipofuscin granules which are responsible for the pigmented sweat (Kavoussi, 2013).

The mechanism of action of BT-A in chromhidrosis is by inhibiting the expression of adrenergic receptors and blocking the release of norepinephrine and substance P because the apocrine glands are unresponsive to cholinergic stimulation (Liu, 2009).

Many case reports showed the effectiveness of BT-A in treating chromhidrosis, the effect of BT-A in all reports was noted within 7 days and the effect was maintained for up to 4 months (Swartling et al., 2002; Wollina, 2002; Pérez-Tato, 2012).

3.3.5. Inverse psoriasis

Inverse psoriasis or flexural psoriasis is a form of psoriasis that involves the skin folds and flexor surfaces such as the axillae and groins.

Because this variant of psoriasis is exacerbated by humidity and sweating BT-A has been tried to treat this type of Psoriasis.

BT-A in Inverse psoriasis may act at the neuroglandular junction level to reduce local sweating with its consequent skin maceration and secondary infection and at the extra-junction level to inhibit the liberation of neuropeptides and other pro-allogenic substances responsible for inflammation and hyperkeratosis.

Fifteen patients with a confirmed diagnosis of inverse psoriasis were enrolled into one study. The psoriasis was located in several areas , a total dosage of BT-A between 50 and 100 U per patient depending on the extent and severity of the psoriasis was injected, Subjective symptomatology improved in all patients and erythema extension, intensity and infiltration improved in 13 of 15 patients (87%). Treatment was well tolerated with no reported adverse events (Aoki, 1962).

The same result was seen in one patient treated with BT-A for inverse psoriasis in his axillae which was completely cleared within 4 weeks (Pérez-Tato, 2012).

Few additional skin conditions such as Granulosis rubra nasi (Matarasso, 2005), pitted keratolysis (Wu et al., 2005), and Eccrine Angiomatous Hamartoma (Zanchi et al., 2008), have been mentioned to show a favorable response to BT-A injection, but because the efficacy of BT-A was evaluated in only a single case report for each condition, we will not discuss the details of these diseases.

3.3.6. Bromhidrosis

Axillary bromhidrosis means the offensive odor that arises from apocrine glands, it is a common problem that causes a serious personal and social handicap. The

mechanism of action in this condition is the same with chromhidrosis since in both conditions the origin of sweating is the apocrine glands.

Sixty-seven patients with axillary bromhidrosis were injected intracutaneously with 50 U of BTX-A into each axilla. After BT-A injection, the malodor was eliminated in 73% of patients (Saber, 2011).

In a randomized double-blinded study 16 healthy volunteers were injected with Botulinum toxin A (Abobotulinumtoxin A) in one axilla and 0.9% sodium chloride solution in the other axilla in, after 7 days a significant reduction of odor intensity was observed for the Botulinum toxin A-treated side (Grazziotin, 2009).

In a different case report there was an improvement of localized foul odor in the genital hair bearing area in one patient who was treated with Botulinum toxin A (Tamura, 2004). Although the offensive odor in the genital area is multifactorial in which hyperhidrosis and bromhidrosis cause part of the problem personal hygiene and bacterial over activity play an important role in this condition.

3.4. Pain and Itchiness related disorders

3.4.1. Post-herpetic Neuralgia

Post-herpetic Neuralgia (PHN) is the most common neurologic complication of Herpes Zoster which is defined as pain persisting beyond 4 weeks, occurred in 16% of patients younger than 60 years but in 47% of those older than 60 years (Barco, 2009).

BT-A has been widely used in many clinical neuropathic disorders including migraine, trigeminal neuralgia, etc. based on these studies BT-A use in neuropathic pain was reported in many randomized, double-blind, placebo-controlled trials and case reports.

30 adults with PHN were randomized either to BT-A or placebo. Severity of pain was evaluated by patients using a visual analogue scale (VAS) and quality of sleep was assessed using a 5-item questionnaire. Thirteen patients from the experimental arm achieved an at least 50% reduction in VAS score, compared with none of the placebo patients. BTX-A patients showed a significant reduction in sleep scores between baseline and week 2, which remained unchanged until 16th week (He et al., 2012).

The therapeutic benefits of BT-A were investigated in subjects with PHN in another randomized, double-blind, placebo-controlled study. Sixty subjects with PHN were randomly and evenly distributed into BTX-A, lidocaine, and placebo groups.

After randomization, one of the following solutions was injecting subcutaneously in the affected dermatome: 5 u/mL BTX-A, 0.5% lidocaine, or 0.9% saline (placebo). Visual analog scale (VAS) pain and sleeping time (hours) were evaluated at the time of pretreatment, day 1, day 7, and 3 months post treatment.

There was a significant reduction in the pain and sleep time in the BT-A treated group in comparison to the

lidocaine and placebo groups (Heckmann et al., 2003). The same results were seen in many case reports (Lee, 2004; Watson and Evans, 1986).

3.4.2. Lichen simplex chronicus (LSC)

LSC is an eczematous dermatosis characterized by intense localized pruritus. The sensation of pruritus in LSC has been shown recently to be related to acetylcholine sensitive C-fibers.

Only single study was published regarding the use of BT-A for LSC, in this study Botulinum toxin type A (Abobotulinumtoxin A) was injected intradermally into 5 lesions in 3 patients, no corticosteroids or any other specific topical therapy was administered, Pruritus subsided within 3 to 7 days in all 3 patients, Within 2 to 4 weeks all lesions cleared completely and no recurrences were noted over a 4-month follow-up (Apalla et al., 2013). Therapeutic efficacy of BT-A as an antipruritic agent in LSC needs larger placebo-controlled randomized trials.

3.4.3. Raynaud Syndrome

Raynaud Syndrome is a vasospastic disorder of the fingers, toes, and other body sites often associated with exposure to cold temperatures or emotional stress, leading to persistent pain and ulceration.

Raynaud's phenomenon usually presented clinically as a digital pain which is associated with sequential pallor, cyanosis, and erythema, and less commonly, acral ulceration. Following a precipitating vasoconstricting stimulus, small-caliber digital arteries undergo an exaggerated response of vasospasm. This decreases blood flow and the digits appear ischemic or white. As the trapped blood becomes increasingly deoxygenated, the digits will then turn cyanotic or blue, and finally red following reperfusion hyperemia.

Cutaneous vasoconstriction and vasodilation are regulated by modulation of sympathetic and parasympathetic neuronal inputs and the complex actions of released acetylcholine (Ach), noradrenaline (NE), peptides, and small molecules such as nitric oxide on vascular smooth muscle.

The mechanism of action of BT-A in Raynaud's phenomenon

Local BT-A injection consistently shows an ability to improve perfusion of the injected tissue by both substantial opening of the vascular bed by inhibiting expression of adrenergic receptors in the vessel wall and blocking the release of norepinephrine and substance P, glutamate, and calcitonin gene-releasing peptide (Xiao et al., 2010).

Since 2004, there have been a lot of studies that have evaluated the use of Botulinum toxin A for the treatment of Raynaud's. All showed overall improvement in patient pain as well as a reduction in soft tissue ulceration (Sotiriou, 2009).

Most of these studies are case series (Liu, 2006; Heckmann et al., 2002; Kossintseva et al., 2011; Iorio et al., 2012; Serri et al., 2013), one is randomized controlled trial (Neumeister, 2010) and two case reports (Neumeister et al., 2009; Fregene et al., 2009) (Table 3). In all of these studies the patients were presented with chronic ischemic hand pain, ulceration and loss of function.

The efficacy of BT-A in treating these patients was by measuring the level of pain, cutaneous temperatures, color, and ulcerations before and after the injection. The range of the dose was 50–100 u per each hand injected in most of these studies following the distribution of the superficial palmar arch (Fig. 4).

Most of the patients in all of these studies experienced improved vascularity (tissue perfusion), relief of pain and ulcerations, most of the patients remained pain-free for many months.

Table 3

Summary of the studies that were made to evaluate the effect of BT-A in cases of Raynaud's phenomenon.

Study	No. of patients	Results
Serri et al. (2013)	18 pts with systemic sclerosis	Thirty days after injection, complete healing of ulcers occurred and the symptomatology significantly improved
Neumeister (2010)	A total of 33 pts (14 men and 19 women)	All but 5 patients experienced improved vascularity and relief of pain
Neumeister et al. (2009)	19 pts	84% reported pain reduction at rest and improvement of the perfusion and ulcerations
Fregene et al. (2009)	26 pts	Statistically significant improvements were noted for pain score and digit transcutaneous oxygen saturation
Van Beek et al. (2007)	11 patients	All patients reported highly significant pain reduction and 9 pts with ulcers spontaneously healed
Kossintseva (2008)	One patient	The BT-A treated hand had reduced swelling, color change, and pain, whereas the untreated control hand remained affected
Jenkins (2013)	10 pts randomized controlled study	There was a significant increase in digital pulp temperatures of the hands treated with and there was no statistically significant difference in cold recovery times between the digits of treatment and control hands
Smith (2012)	Single female pt	There was an immediate decrease in pain after administration of BT-A along with a rapid and prolonged increase in tissue perfusion lasting months to years

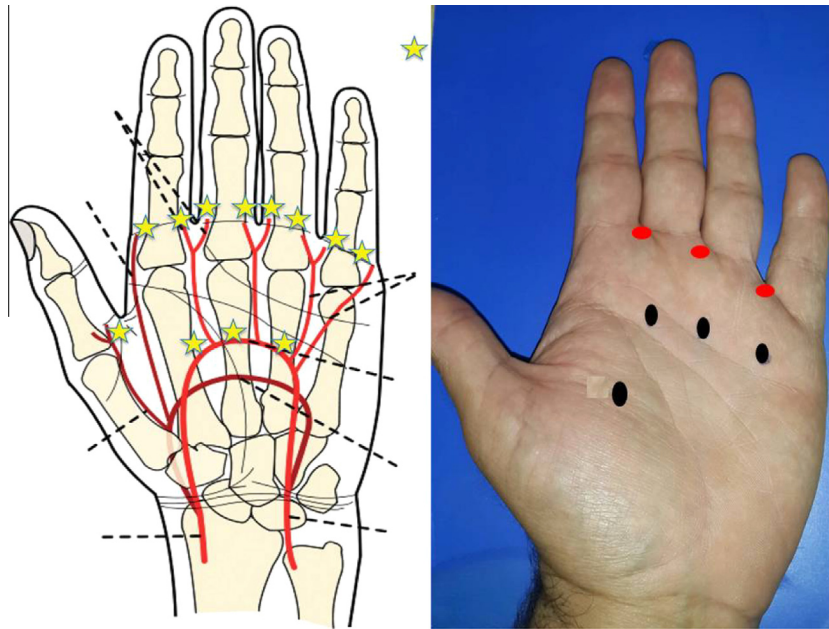


Figure 4. Injection of Botulinum toxin-A in Raynaud Syndrome into the web spaces (red dots) and around neurovascular bundles (blue dots).

4. Conclusion

BT-A was found to be a safe and effective therapy without significant local or systemic side effects. Although it is FDA approved in certain conditions, it has been used as an off-label modality of treatment in many skin diseases; most of these conditions are either exacerbated by excess sweating or they are pain related disorders and most of these disorders are resistant to many different treatment ways.

Based on this we advise not to use BT-A routinely in the conditions that were discussed earlier in this article, since the use of BT-A in these off-label conditions needs larger and randomized controlled trials, but keep this modality of treatment as the last option when the regular modalities of treatment fail or there is a clear contraindication to use.

Conflict of interest

None declared.

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