

Use of Botulinum Toxin in Treatment of Acne Vulgaris

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Abstract

Background: *Acne vulgaris* is a common inflammatory disorder involving the pilosebaceous unit. The pathogenesis is multifactorial, involving four key factors with interrelated mechanisms: increased sebum production, hyperkeratinization of the follicular infundibulum, inflammation, and *Cutibacterium acnes*. Botulinum toxin (BoNT) is a potent neurotoxin protein derived from the *Clostridium botulinum* bacterium. It exerts its effect at the neuromuscular junction by inhibiting the release of acetylcholine, which causes temporary chemical denervation. At the cellular level, botulinum toxin functions by cleaving a synaptic protein (synaptosomal-associated protein of 25 kDa [SNAP-25]) on the internal surface of neuronal membranes, thereby inhibiting vesicle fusion and release of acetylcholine.

Keywords: *Acne Vulgaris, Botulinum Toxin.*

INTRODUCTION

Acne is a chronic inflammatory skin condition seen commonly in adolescence and young adulthood. Despite being a frequent and nonthreatening life condition, acne has a significant psychological impact and comorbidity which requires effective treatment to improve the patient's skin and self-esteem (1). Delayed treatment and severity of acne are associated with a greater extent and severity of scarring. Acne scarring has been categorized into increased tissue formation (including hypertrophic and keloid scars) and more commonly loss of tissue (including ice pick, rolling, and boxcar type scars) (2).

Epidemiology:

Acne is a very common skin disease with the prevalence among adolescent is 80% or more, among them 80% are teenagers (3).

Approximately 80% to 90% of teenagers in the Western world experience behavioral/emotional and physical/psychological effects caused by acne. About 60% of affected adolescents have mild acne for which they use non-prescription preparations without consulting a physician. The remaining 40% constitute the population of acne patients seen in medical practice. It is less common in African-Americans and Asians than in the Caucasian population. About 20% of the affected individuals develop severe acne which results in scarring. In youths, overweight and obesity are inversely associated with acne in a dose-dependent manner, specially in girls aged 18 and 19. (3).

Etiology:

The pathogenesis is multifactorial with four primary pathogenic factors including: (a) abnormal hyperkeratinization of the pilosebaceous duct with comedo formation caused by increased androgens; (b) an increase in sebum production from the enlarged sebaceous gland caused by increased androgens; (c) colonization and proliferation of the duct with bacteria, most commonly *P. acnes*, although clear evidence of a causal relationship between *P. acnes* and AV is lacking; and (d) an inflammatory response caused by the immunological activity of *P. acnes* (4).

Pathophysiology

Acne is proposed to be an IGF-1-mediated disease, modified by diets and smoking increasing insulin/IGF1-signalling (5). The main hormones responsible for the development of AV include androgens, insulin and insulin-like growth factor-1. Other factors involved in this process are corticotropin-releasing hormone, α -melanocyte-stimulating hormone and substance P (6).

During puberty, alteration of the sebaceous lipid profile, called dysmenorrhea, stress, irritation, cosmetics and potential dietary factors lead to inflammation and formation of different types of acne lesions (7). Distended follicles rupture and release proinflammatory chemicals into the dermis, stimulating inflammation. *P. acnes*, *Staphylococcus epidermis* and *Malassezia furfur* induce inflammation and induce follicular epidermal proliferation (8).

The most commonly discussed pathology relating to the sebaceous gland is acne vulgaris. Some estimate that up to 80% of people will experience acne at some point during their lifetime. The pathogenesis of acne is complex, with the sebaceous gland playing a prominent role(8).

Clinical Diagnosis

Acne lesions typically occur on the face, chest, or upper back. The lesions may be noninflammatory closed comedones (i.e., papules formed by the accumulation of sebum/keratin within the hair follicle; also called whiteheads); open comedones (i.e., distension of the hair follicle with keratin leads to opening of the follicle, oxidation of lipids, and deposition of melanin; also called blackheads); or inflammatory papules, nodules, pustules, and cysts. Inflammatory lesions result from follicle rupture triggering an inflammatory response. Based on the extent and types of lesions, acne severity may be classified as mild, moderate, or severe (9).

The diagnosis of AV is primarily clinical. The common differential diagnosis of acne includes folliculitis, keratosis pilaris, perioral dermatitis, seborrheic dermatitis and rosacea. History and physical examination can help determine if there is an underlying cause of the acne, such as an exacerbating medication or endocrinologic abnormality causing hyperandrogenism (e.g., polycystic ovarian syndrome)(3).

Management of Acne Vulgaris

Due to better understanding of the pathogenesis of acne, new therapeutic modalities and various permutation and combinations have been designed. In topical agents; benzoyl peroxide, antibiotics, retinoids, etc., are the mainstay of treatment; can be given in combinations. While systemic therapy includes oral antibiotics, hormonal therapy and isotretinoin, depending upon the need of patients it has to be selected. Physical treatment in the form of lesion removal, phototherapy is also helpful in few of them(3).

Acne Prevention:

The relationship between diet and acne is highly controversial. Several studies during the last decade have led dermatologists to reflect on a potential link between diet and acne. Selected dietary factors on the course of AV are milk and dairy products, chocolate, glycemic load of the diet, dietary fiber, fatty acids, antioxidants, zinc, vitamin A and iodine (3).

Milk and dairy products:

High intakes (≥ 2 glasses/day) of full-fat dairy products were associated with moderate to severe acne. No significant associations were found between acne and intake of semi-skimmed or skimmed dairy products, and not with moderate intakes of any fat variety of dairy products. Also, no significant association between yogurt/cheese and acne development (9).

Acne that occurs after ingestion of foods rich in iodine appears suddenly and is characterized by many papules. The association between acne and milk may also be a result of the iodine content of milk (10).

Chocolate restriction:

Slawson., (11) found a statistically significant increase in facial acne lesions among college students 48 hours after ingesting chocolate instead of jellybeans.

Dark chocolate contains more antioxidants than milk chocolate, which would lead to conclusion that it may have much smaller comedogenic effects

Glycemic load:

A high glycemic index (GI) and glycemic load (GL) diet may stimulate acne proliferative pathways by influencing biochemical factors associated with acne. A low GI and GL diet decreased IGF-1 concentrations, a well-established factor in acne pathogenesis. Having fast food like fries/chips and soda can dramatically increase the calories, carbohydrate, fat, and GL and promote acne development (12).

Dietary fiber:

Some soluble dietary fiber components, such as oat bran, pectin and guar gum, stimulate fecal excretion of bile acids. High fiber intakes promote increased bacterial mass but do not alter the microflora composition. Gastrointestinal dysfunction is an important risk factor for diseases of the sebaceous glands and is correlated with their occurrence and development (13).

Topical Drugs:

Topical treatment is the mainstay of acne therapy. The most commonly prescribed topical medications for acne include benzoyl peroxide, clindamycin and retinoids. Despite their effectiveness in treating mild to moderate acne vulgaris, these topical medications are found to be irritating and are historically associated with poor tolerability and diminished patient adherence. Thus, choosing the right formulation that will be effective and well tolerated is essential (3).

Benzoyl peroxide

Benzoyl peroxide (BP) has been an important component of topical therapy for acne vulgaris for more than five decades due to its ability to markedly reduce *Propionibacterium acnes* and inflammatory acne lesions and its ability to moderately reduce non-inflammatory acne lesions. It has mild sebostatic and keratolytic effects without a concern for the development of drug-resistant bacteria. It is most effective when used in combination with other acne vulgaris therapies. BP is a bactericidal agent. Combining BP with a topical antibiotic in a stable formulation has been proven in clinical trials to reduce total P acnes count by 99.7% after 1 week of therapy, eliminating both susceptible and resistant strains of P. acnes. However, we have recently noticed BP's benefits as monotherapy in the treatment of acne. Topical BP also has mild sebostatic effects contributing to its keratolytic activity and efficacy in treating comedonal acne. BP is available as both over the counter and prescription formulations in concentrations of 2.5%, 5% and 10% (14).

Clindamycin

Clindamycin can be administered into the body by multiple routes. It is available topically as a foam, gel, lotion or solution for treatment of acne vulgaris. The most common side effects experienced with topical use include pruritis, xeroderma, erythema, burning, exfoliation or oily skin (15).

Retinoids

Topical retinoids are creams, lotions and gels containing medicine derived from Vitamin A. These compounds result in proliferation and reduced keratinization of skin cells independent of their functions as

a vitamin and devoid of bacterial resistance. American Academy of Dermatology (AAD) states “retinoids are the core of topical therapy for acne because they are comedolytic, resolve the precursor microcomedone lesion and are anti-inflammatory;” further, they “allow for maintenance of clearance” (16).

Local adverse effects, including erythema, dryness, itching, and stinging, occur frequently during the early treatment phase. Their impact varies with the vehicle formation, skin type, frequency and mode of application, use of moisturizers and environmental factors such as sun exposure or temperature (17).

Retinoids act to normalize desquamation by reducing keratinocyte proliferation and promoting differentiation. Isotretinoin, tretinoin and tazarotene also suppress Toll-like receptor expression. Blocking these pathways reduces the release of inflammatory cytokines and nitric oxide and inhibits cellular inflammation (16).

Topical retinoids are safe and efficacious for the treatment of AV. They should be used in combination with benzoyl peroxide to optimize results in patients. Adapalene has a superior tolerability profile amongst topical retinoids (16).

Laser Therapy

Laser therapies are increasingly becoming part of or an adjunct to the medical treatment of active acne and are a useful treatment modality. Studies of lasers in the treatment of acne, including erbium glass, Nd:YAG, pulse dye laser (PDL), potassium titanyl phosphate (KTP) laser, and laser-based photodynamic therapy, have been published (18).

Laser therapy is advantageous because it is an in-office treatment, which ensures patient adherence to therapy. In addition, it offers no systemic side effects that might complicate treatment when using oral acne medications (18).

Management of acne scars

Scars are important permanent sequelae of acne. Up to 95% of patients with acne have scars, with 30% developing severe scars (19).

None of the currently available treatments achieve complete resolution of scars. Prevention of scars by early and aggressive acne treatment remains the best option. There are numerous medical, surgical and procedural options that can help to achieve profound cosmetic improvement in acne scars. Using these methods in combination can even be more successful (20).

There are two main types of acne scars depending on the tissue response to inflammation: scars caused by increased tissue formation (hypertrophic and keloidal scars) and scars caused by loss of tissue (atrophic scars). Atrophic acne scars are more common than keloids and hypertrophic scars, and can be divided into three subtypes: icepick or V-shaped, rolling or M-shaped and boxcar or U-shaped. Keloidal scars are more common in darker-skinned individuals (20).

Other treatment options might be applied to the entire affected area, including chemical peels, laser therapy or dermabrasion. With the advent of laser resurfacing, dermabrasion is now used less frequently. Topical retinoids used with procedures improve results and reduce the risk of changes in pigmentation (21).

PDL is effective in improving the vascularity, pliability, color, and height of hypertrophic scars and keloids. Previous studies have reported a 57% to 83% improvement in clinical appearance and texture of hypertrophic scars after one to two PDL treatments (22).

Non-ablative fractional lasers (NAFL) have been shown to significantly improve the pigmentation and thickness of surgical scars, atrophic scars, hypertrophic scars and hypopigmented scars (22).

Botulinum Toxin

Cosmetic uses of botulinum toxin

Botox injected directly into the target muscle, treats vertical lines between the eyebrows, the squint lines or crow's feet at the corners of the eyes, the forehead horizontal lines and the platysmal muscle bands. Once the muscle is weakened and relaxed, it cannot contract. Since there is no way to make the undesirable facial expression, the lines gradually smooth out from disuse, and new creases are prevented from forming. The wrinkle-preventing effect of Botox normally lasts about 3-4 months, but can last up to 6 months (23).

1. Lateral Orbital Region (Crow's Feet)

Injector should be kept one–two cm away from the orbital margin to target the orbital subdivision of the orbicularis oculi muscle. Injection sites typically range from 3 to 5 per side with total starting doses of 8–16 and 12–16 units of Botox Cosmetic per side in women and men, respectively. In patients with lax lower eyelids, caution should be used when injecting medially to avoid disrupting proper lid function (24).

It is prescribed the doctor positions inverse to the injected side, so that the needle focuses far from the patient's eyes. The doctor ought to utilize ideal lighting and extend the skin marginally to abstain from infusing into veins. To maintain a strategic distance from ecchymosis, infusion ought to be exceptionally shallow and applying ice previously, then after the fact infusion may likewise be useful. Profound infusion or infusion into the mediocre locale of the zygomaticus major ought to be maintained a strategic distance from, as it might prompt undesirable impacts, for example, hanging mouth corners (24).

The most oftentimes reported treatment-related unfriendly occasion was gentle periorbital haematoma. Eyelid ptosis can be stayed away from by infusing externally and utilizing the insignificant infusion measurements and volume(25).

Few complications occur during treatment of crow's feet for example ectropion, diplopia, strabismus, and eyelid ptosis can happen. To avoid these obstacles, caused by effects of the toxins to extraocular muscle and palpebral portion of the orbicularis oculi muscle one cm away from the lateral orbital rim should be done (25).

2. Lower eyelid wrinkle.

Injections are done at the midpupillary line three mm howl the ciliary edge and if a second point is essential, it could be put one cm along the side from the first. Every point can be infused with one U of onabotulinum toxin and one-two and half U of abobotulinum toxin (26).

3. Glabellar line

The management of glabellar lines, there are 5 points infusions are prescribed with 1 point in the procerus and 2 focuses on each corrugator focuses ought to be one centimeters from the upper orbital edges and inner to the mid-pupillary lines (27).

Infusion ought to be opposite, intramuscular and profound to the last third of a thirty gauge needle. The suggested all out measurements is fifty subunits similarly appropriated among the 5 infusion focuses, with ten subunit (0.05 mL)/point (27).

4. Horizontal forehead lines

There are 4 to 8 points of one–four unit of ONA/INCO or five–ten unit of abobotulinum toxin each are utilized for infusion of the brow, contingent upon whether it is chosen to treat the temple totally or partially. The focuses are for the most part circulated on a level plane, more alluring in men or in an "Angular shape," ordinarily attractive in women. Little measurements are suggested and restricted infusion focuses, to maintain a strategic distance from a solidified look. It is imperative that all infusions

are produced using one to two cm over the orbital edge, with a specific end goal to evade eyebrow ptosis, which causes a drained appearance (26).

5. Bunny lines and drooping nasal tip

Botulinum poison- A is utilized as a part of the transversal regions of the nasalis muscles. The infusion point ought to happen on the upper 33% of the nose, on the average part of the sidewall with a specific end goal to stay away from the vein and levator labii superioris alaeque nasi muscle, which may prompt ptosis of the upper lip (28).

Low measurements, for example, two units of onabotulinum toxin or five units of abobotulinum toxin are in every side (29).

6. Perioral wrinkles

In the treatment of perioral wrinkles, four–six infusion focuses are prescribed, Average focuses ought to be one mm far from the philtrum. An aggregate measurement of four–twelve subunits is prescribed, with one to two subunits for each point. The measurements rely on upon the muscle quality, seriousness of the dynamic wrinkles and the level of elastosis. Infusion ought to be opposite to the skin and externally intramuscular, to the principal third of the needle (24).

7. Dimpled chin

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