

Paradoxes in Aesthetic Dermatology

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Abstract

Background: Various paradoxical phenomena related to aesthetic dermatology including paradoxes of Q-switched laser-induced tattoo darkening, intense pulsed light (IPL) and laser-induced hypertrichosis, paradoxical adipose hyperplasia of post-cryolipolysis, paradoxes of androgenetic alopecia, sebaceous glands and aging skin, paradox of acne fulminans associated with isotretinoin treatment, paradoxical rosacea with topical calcineurin inhibitors, paradoxical erythema associated with brimonidine gel, paradoxical masseteric bulging, wrinkles and alopecia associated with botulinum toxins, paraben, lanolin, nail lacquer, exogenous ochronosis paradoxes have been described in the literature. While some of them can be explained logically, the cause for others can only be speculated. Whenever encountered in clinical practice, background knowledge of such paradoxes may be useful to the clinician. As reported previously, when paradoxes are suspected after aesthetic procedures, these therapies should be discontinued and the other alternative procedures are recommended.

Introduction

A “paradox” is defined as a “seemingly absurd or contradictory statement or proposition which when investigated may prove to be well founded or true according to Oxford dictionary[1]. We can call these conditions as the Janus effect (two faces of aesthetic dermatologic treatments), Yin/Yang effect or Dual effects. There are some well-known paradoxes in aesthetic dermatology, some of which can be explained logically or based on evidence, while for some, only assumptions or postulates are put forth. Following are some of such paradoxes in aesthetic dermatology compiled under characteristics (Table 1), [1, 12,13,14,15].

Paradox of Androgenetic alopecia: At puberty, the beard and other secondary sexual hairs grow, the scalp hair is gradually lost,

while the eyebrows and eyelashes remain unchanged. This paradoxical effect of androgen at different hair bearing sites is attributed to the differential[1]. Response of the follicular dermal papillae to androgen stimulation in these sites. In response to androgen stimulation, the dermal papillae in the beard region secretes IGF1, which has a stimulatory effect on the hair follicles. On the scalp area, it secretes TGF-β1 that has an inhibitory effect on the hair follicles. TGF-β1 activity is maximum in the anterior aspect of the scalp, especially so, over the temples and hence, the development of “patterned” hair loss[3].

Paradox of Sebaceous glands in aging skin:

In the elderly, in spite of decreased output from sebaceous glands, which is attributed to decreased adrenal and gonadal androgen synthesis. Their size however, is increased owing to decreased cell turnover[15].

Paradox of Aging Skin: In chronologically aging skin, the elastic fibers gradually lessen, most likely due to enzymatic degradation of elastin. Together with decreased elastin, the skin becomes wrinkled, saggy, and inelastic, due to decreased collagen synthesis. Paradoxically, the photo-aged skin shows focally increased elastin owing to UV-induced transcriptional activation of the elastin gene and lysozyme-induced reduction in leukocyte elastase activity. Together with heliodermatitis, photo-aged skin appears thick, dry, rough, deeply wrinkled, and inelastic owing to the disarrangement of collagen and elastic fibers[16].

Isotretinoin and acne fulminans: Acne fulminans is a severe form of acne with systemic features, that may occur in some predisposed individuals as a hypersensitivity reaction to Propionibacterium acnes. The treatment of choice is a sequential therapy beginning with

systemic corticosteroids to combat the early crisis followed by systemic doxycycline in addition of low-dose oral isotretinoin for 3-4 months with the steroids being tapered off gradually. However, isotretinoin must be used with caution, as paradoxical induction/exacerbation of acne fulminans has been reported[17,18].

Paradoxical topical calcineurin inhibitors (TCIs)-induced rosacea: TCIs are relatively newer topical treatment modalities used for the treatment of rosacea. However, reports of rosaceiform dermatitis following long-term usage of these agents have also been documented. Topical immunosuppressive effects of the TCIs leading to overgrowth of Demodex mites in skin together with their inherent vasoactive properties possibly act synergistically leading to “iatrogenic rosacea. In this condition, oral doxycycline, minocycline, clindamycin, metronidazole or lymecycline treatments are recommended[19].

Table 1. Paradoxes in Aesthetic Dermatology

Paradoxes	Treatments
Paradox of Androgenetic Alopecia	Hair transplantation, topical minoxidil, finasteride dutasteride
Paradox of Sebaceous glands in aging skin	Surgery, cryotherapy, electrocoterisation, peeling, lasers
Paradox of Aging Skin	Surgery, cryotherapy, electrocoterisation, chemical peeling, lasers, topical retinoids, topical sunscreens
Paradox of isotretinoin and acne fulminans	Systemic corticosteroids and oral antibiotics
Paradoxical topical calcineurin inhibitors (TCIs)-induced rosacea	Oral doxycycline, minocycline, clindamycin, metronidazole or lymecycline
Paradoxical Erythema Reaction of Long-term Topical Brimonidine Gel for the Treatment of Facial Erythema of Rosacea	Lasers, topical sunscreens, oxymetazoline cream
Paradoxical Q-switched laser-induced tattoo darkening	Other lasers like picosecond 532nm and 1,064 nm laser
Paradoxical hypertrichosis [20].	Other lasers
Paradoxical Adipose Hyperplasia After Cryolipolysis	Surgical treatment (liposuction or abdominoplasty) or deoxycholic acid injection
Paraben, lanolin and nail lacquer paradoxes	Therapy should be discontinued
Exogenous ochronosis paradox	Other bleaching agents
Paradoxical Masseteric Bulging after BTXA	5-10 U injection over superficial masseter
Paradoxal Wrinkles after forehead BTXA	Additional botulinum toxin injection at hyperactivated muscles
Paradoxal Frontal Alopecia after Repeated BTXA	Therapy should be discontinued [2,3,4,5,6,7,8,9,10,11,12,1,3,14,15]

Paradoxical Erythema Reaction of Long-term Topical Brimonidine Gel for the Treatment of Facial Erythema of Rosacea:

In 2013 brimonidine tartrate gel 0.33% was approved by the FDA for the treatment of facial erythema of rosacea. Highly selective α -2 adrenergic agonist, when applied topically it causes peripheral vasoconstriction via a direct effect on the smooth-muscle sheath of superficial cutaneous blood vessels. The blanching effects last 10-12 hours at which point the patient is expected to return to baseline erythema. It was reported a case of facial erythema of rosacea that responded to brimonidine gel with effective blanching for two years until the patient developed a paradoxical erythema reaction. This is an side effect physicians should be aware of with continued prescription of brimonidine gel for their rosacea patients[13].

Paradoxical Q-switched laser-induced tattoo darkening:

Paradoxical darkening of the tattoos, especially the red, white, or flesh-toned ones (pink, yellow, tan) occur occasionally. These tattoo pigments often contain ferric oxide (rust-brown) and titanium dioxide (white). Following laser treatment, these pigments get reduced to ferrous oxide (black) and blue-colored titanium dioxide respectively. Increased pigmentation may be caused by deposition of melanin or haemosiderin as well as melanocyte stimulation. Hyperpigmentation was also reported after Q-switched YAG laser treatments for congenital pigmented naevus and melasma. Q-switched laser treatments are contraindicated in patients who have received gold therapy as they induce chrysiasis. Other lasers like picosecond 532 nm and 1,064 nm lasers are recommended as treatment[8].

Paradoxical Hypertrichosis

It can occur after all laser/IPL treatments for hair removal [20]. Choosing an appropriate treatment modality, wavelength, and pulse width and fluence to deliver the wavelength at, are all imperative for optimal treatment outcome, as paradoxical hypertrichosis has been observed after laser treatment. Paradoxical hypertrichosis has a low incidence (0.6-10%), and most commonly occurs on the face

and neck. It occurs especially in individuals with darker skin types (III-VI); with dark, thick hair; and with underlying hormonal conditions. Higher hair density, darker color, coarseness, or a combination of these at treated sites are risk factors for paradoxical hypertrichosis. In this condition, there should be the absence of any other known cause of hypertrichosis[7,21,22].

Moreno-Arias et al, first described paradoxical hypertrichosis in five of 49 females with PCOS undergoing IPL treatment for facial hirsutism. *Moreno-Arias* and colleagues also defined paradoxical hypertrichosis as the growth of hair in untreated areas in close proximity to treated areas[23].

Hirsch et al, reported the paradoxical effect in 14 patients treated with the long-pulse 755-nm alexandrite laser. Terminal hair has been observed to appear especially in areas of vellus hair growth[21,22].

Marayannis et al showed that hair induction occurred several months after the onset of laser hair removal treatments and after at least three treatments had been performed. This indicates that hair induction is a process that develops over time and that some type of local activation is necessary[24].

Etiophysiological mechanisms: Inflammation and inflammatory mediators (prostaglandins and thymosin β 4 which promotes angiogenesis and wound healing), subtherapeutic thermal injury (more angiogenesis and acceleration of hair cycling), hyperemia, immobilization and reflex sympathetic stimulation are suspected. The heat-induced inflammatory reaction that occurs in the follicular papilla, with an increase in the blood flow supply and growth factors for the follicle, might also play a role. The heat shock may induce follicular stem cell differentiation and growth by increasing the level of HSPs like HSP 27 in the tissue involved in the regulation of cell growth and differentiation. They believed that a better understanding of paradoxical hypertrichosis may also be useful in the treatment of alopecia[22].

Perifollicular inflammation associated with photoepilation persists for up to 2 weeks. Although feasible, this idea does not explain why some follicles react in this way and others do not, because inflammation is not selective

and thus is not limited to less thermally injured areas. Another hypothesis is that the process of laser epilation may serve to synchronize the cycling of hairs growing within the laser treatment sites. For example, if all hairs within a given area are simultaneously in anagen, the overall hair density may appear to be greater than when hair cycling is asynchronous[23].

Contributing Factors

1. Hair thickness: Thicker hair is easier to heat, whereas thinner hair, which contains less chromophore, absorbs light energy less efficiently and is more difficult to heat. This explains the failure to epilate fine hairs on the face, abdomen, linea alba, and back and shoulders in men.
2. Hair color: Melanin is the chromophore absorbed during photoepilation. As a result, darker hair is more efficiently heated.
3. Depth of treated hair: The optical penetration of light may be too superficial to adequately thermally injure deeply growing anagen hairs.
4. Underlying undiagnosed hormonal conditions; PCOS and associated ovarian hyperandrogenism.
5. Hormone supplements
6. Medications inducing hypertrichosis; Corticosteroids and finasteride.
7. The incidence of vigorous laser and IPL post-treatment side effects; erythema, crusting, edema, hyperpigmentation
8. Treatment with suboptimal fluences; when there is insufficient light energy to destroy melanocytes in the matrix of the follicle.
9. Anatomical site/sex: Face and neck of women were most likely.
10. Skin types III to VI (as a result of the greater likelihood of a shift between vellus and terminal hair in patients of darker skin types)[7,9].

Associated Lasers: Paradoxical hypertrichosis, first reported with IPL therapy in 51 of 991 patients. *Hirsch* et al described it in 14 patients who were treated with a long-pulse

755-nm alexandrite laser. *Willey* et al also observed that the 694-nm ruby, 755-nm alexandrite, 810-nm diode lasers caused hair induction. It is unclear whether hair removal with the 1,064-nm Nd:YAG laser is less likely to cause hair stimulation or if it is simply used less often, as is the case in their practice. Paradoxical hair growth has also been reported when IPL systems are used for other indications such as tattoo and a port-wine stain. It was reported also the postradiotherapy hypertrichosis and low-level radiant exposure by home-use laser and intense pulsed light devices hypertrichosis[20,21,22,23,24,25].

Treatment Protocols: Therapy is based on two facets: treatment of the already present induced hair and the prevention of hair induction. Several researchers suggest the continuation of treatments and inclusion of the new hairy areas in the treatment areas, because induced hair responds to treatment in the same manner as other hair follicles. After a few treatments, all of the unwanted hair should be gone. Using a shorter-cut filter may also help in this matter, but to prevent the paradoxical effect, the use of higher laser fluences is widely emphasized. *Willey* et al recommend the placement of cold packs surrounding the treatment area during laser therapy to prevent low energies from reaching peripheral follicles. The researchers further recommend making 2 passes with the laser during treatments. Long-pulse 755-nm Alexandrite laser, 18-mm spot size with an energy setting of 12 to 14 J/cm² followed by a second pass using 8 to 10 J/cm² 1 minute later. Alternatively, a single treatment using one pass followed by a second single-pass treatment 1 week later may be tried. Another suggestion is to decrease the amount of time between laser treatments. *Willey* et al noted that terminal hair growth most often occurred between the third and fourth treatments but also occurred as late as after the tenth treatment. The most cases of terminal hair growth occurred when treatment intervals were more than 8 weeks apart[25]. *Schroeter* et al advise that the interval between treatments be between 4 and 6 weeks as 3 sessions with the 1,064-nm Nd:YAG laser, spot size of 10 mm, pulse du-

ration of 30 ms, and energy fluence of 30 J/cm²[26].

Paradoxical Adipose Hyperplasia (PAH) After Cryolipolysis

Although cryolipolysis has a low incidence of side effects, 33 cases of PAH have been reported (0.0051-0.14%). The adipose tissue at the treatment site is reported to increase in mass to a degree that is clearly visible at the macroscopic scale. MRI data revealed growth of the cryolipolysis-treated tissue, while H&E staining revealed decreased adipocyte organization, septal thickening around fat globules, and an increase in vascularity in the cryolipolysis-treated tissue. The methodology takes advantage of the observation that lipid-rich cells are more susceptible to cryoinjury. Typical treatment time is 1 hour, during which the temperature of the tissue roll decreases to about 0°C. Crystallization of cytoplasmic lipids within the adipocytes initiates a cascade of events, characterized by adipocyte apoptosis, panniculitis, and eventual loss of adipocytes. FDA initially approved cryolipolysis for the noninvasive reduction in focal adiposity of the flanks in 2008 and later for the abdomen in 2011, for submental or chin fat area in 2015. Side-effects include temporary erythema, edema, mild pain. Transient decrease in sensation is seen in two-thirds of patients, which can persist for up to 8 weeks[6,27].

Factors mediating susceptibility: Incidence of PAH has been higher in male gender, and in patients of Hispanic descent[27].

Etiology: The negative suction process of the cryolipolysis instrument may stimulate adipocyte proliferation. Suction with inadequate cooling may lead to hypoxia and stimulate reparative rebound adipose hypertrophy and septal thickening. PAH may be due to this fibrosis of the adipose tissue, in which the extracellular matrix is expanding. Some adipocytes may be “naturally selected” for survival due to their inherent tolerance to cryolipolysis. Cryolipolysis leads to activation of pre-existing adipocytes via recruitment of resident or circulating stem cell population[6,27].

Treatment: Cryolipolysis therapy should be discontinued. Surgical treatment (liposuction or abdominoplasty) is recommended. Deoxycholic acid injection also can work[6,27].

Paraben paradox: Many individuals who are allergic (patch test positive) to parabens can continue using cosmetics containing them on normal skin without developing any dermatitis. But react to such topical medications when applied over compromised skin like venous ulcers[4].

Mechanism: Parabens are metabolized by the esterases in epidermis and also paraben-resistant microbial strains hydrolyze parabens to hydroxybenzoic acid. In defective skin, parabens will not metabolize by esterases and also paraben resistant bacteria will hydrolyze parabens to allergic compounds[4].

Lanolin paradox: Lanolin is mostly used in topical medications, emollients, and cosmetics. Lanolin-sensitive patients often are patch test negative to pure lanolin, which may be due to a low concentration of allergens and also the fact that when used “as is,” pure lanolin is a weak sensitizer[5].

Nail lacquers paradox: Contact allergy to nail lacquers is common. Tosylamide/formaldehyde resins are mostly used in lacquers. Allergic contact dermatitis to these resins may occur on any part that are accessible to the nails (commonly the eyelids, face, neck, and occasionally the thighs and genitalia) and paradoxically in many, no signs of dermatitis are seen at the periungual region[14].

Exogenous ochronosis paradox: It is a localized paradoxical hyperpigmentation of the skin due to prolonged use of bleaching agents containing hydroquinone and phenolic compounds. Topical hydroquinone may inhibit homogentisic acid oxidase in the dermis, with the result of a local accumulation of homogentisic acid that polymerizes to form ochronotic pigment. The ochronotic coloration most commonly results from the prolonged use of certain topical agents like hydroquinones, but it also occurs with the use of antimalarials and products containing resorcinol, phenolic compounds, mercury, or picric acid[10].

Paradoxical Masseteric Bulging after Botulinum toxin (BTXA) Injection: Paradoxical masseteric bulging occurs in rare cases after BTXA injections into the masseter (0.49 %). The deep inferior tendon can prevent the toxin from spreading into the entire superficial masseter during the BTXA injection procedure and also superficial masseter muscle

fiber overactivity. In the treatment, 5-10 U injection over superficial masseter is recommended, if not abated after 1-2 weeks[11].

Paradoxal Wrinkles after forehead BTXA Injection: Site specific side effects associated botulinum toxin injection for forehead horizontal lines includes paradoxal exaggeration of wrinkles. The new appearance of a noticeable glabellar protrusion and also, a new deep wrinkle on one side of the forehead just above the eyebrow have been reported. For the treatment of forehead horizontal lines, the injection points should always be 4-5 cm above the orbital rim. As a result, paralysis of the frontalis is limited to the upper part of the frontalis and compensatory hyperactivation of the lower part of frontalis muscle can be possible in the lateral part of forehead. Therefore, especially in people frequently using the frontalis muscle to raise their eyebrows or eyelids, exaggeration of previously unidentifiable wrinkles can take place at the border between the paralyzed frontalis muscle and non-paralyzed frontalis muscle. In the medial part of the forehead, the hyperactivation of glabellar muscles can be possible because of similar reasons. This hyperactivation of glabellar muscles with weakness of the frontalis muscle may cause the protruding of glabellar area. The exaggeration of forehead lines after botulinum toxin treatment can improve spontaneously without any further treatment. For the compliance and satisfaction of patients, additional botulinum toxin injection at hyperactivated muscles can be performed[12].

Paradoxal Frontal Alopecia after Repeated BTXA Injections for Forehead Wrinkles: It was reported the cases of 5 females who developed regression of the frontal hairline after several treatments with BTXA for forehead wrinkles. The authors called this phenomenon as botulin induced frontal alopecia (BIFA). Wabbels and Stanzel reported a patient with eyebrow alopecia following repeated injections of BTXA for blepharospasm. There are 3 studies that evaluated the effectiveness of BTXA injections for the treatment of alopecia areata and androgenetic alopecia with almost poor results. Possible explanations include changes in the levels of molecules that may be involved in regulating the hair cycle, i.e. substance P and calcitonin gene-related peptide and other signaling molecules and receptors, and/or dec-

reased neurological stimulation of hair follicle function due to blockage of the function of autonomic fibers[28,29,30,31,32].

Conclusion

Whenever encountered in clinical practice, background knowledge of such paradoxes may be useful to the clinician. As reported previously, when paradoxes are suspected after aesthetic procedures, these therapies should be discontinued and the other alternative procedures are recommended.

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