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# Minimally invasive Procedures for Facial Rejuvenation

Edited by
Curinga Giuseppe
Rusciani Antonio

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# Minimally Invasive Procedures for Facial Rejuvenation

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# Preface

The requests of procedures aimed to improve the “look” are significantly getting increased recently. A whole series of factors such as the extension of mean life, the quality improvement of it, the extension of the economic well-being for a category of population which go increasing more and more (with ups and downs), the widespread and penetrating development, through mass media, of images, models and lifestyles with a high social impact are some of the responsible factors of this event. An attentive observer cannot notice how less and less people are prepared to submit themselves to immersive, aggressive treatments, some of them executed under general anesthesia. This is certainly to be related to a higher reluctance to accept “the pain” and also to the trust in science and technology maybe excessive.

The security of being able to reach the most with little or no effort is a widespread opinion by now. Let’s consider in this sense the saving and miraculous meaning of what the word “laser” has taken on in the popular imagination.

If these can be the reasons that have produced the success of mini invasive rejuvenation procedures it should be noted that medicine in respecting its professional mandate has been able to give a correct answer to this question according its scientific and cultural tradition.

Inspired by those concepts, a whole range of technologies, drugs, substances, procedures have been studied, selected, well improved, and subjected to continuous development in order to treat facial skin imperfections.

The doctors involved didn’t back out of another task that is under their responsibility and that is to inform, to educate and to spread.

In recent years a lot of conferences and workshop were based on the scientific discussion and training where the new technologies have been analyzed, discussed and taught.

But also many articles and books were born and in this area the new publication has to be considered. It stands out for its own peculiarity of being an e-book and so a book offering a fast and an immediate consultation and theoretically an unlimited circulation.

The e-book wants to be a rational tuning of non-invasive facial rejuvenation techniques. In this sense it was useful to involve some dermatologists and plastic surgeons in the preparation of the work.

Through the encounter of two different sensibilities, mostly conservative for the dermatologist and mainly interventionist for the plastic surgeon, the expositive balance and the objective evaluation of the clear possibility and objective limits of the procedure described, were born.

This later represents the condition of the topic nowadays.

At these elements specialists and also young doctors who come for the first time can draw on. The first will have the possibility of a critical evaluation of the text; the latter shouldn’t make the mistake of considering the subject as a frivolous thing or in a superficial way.

Many people with cancer or in a pre-cancer situation go to the doctor driven not by the suspicion of being bearer of a disease but bearer of something bad to look at. After knowing the diagnosis they are more worried about the scars results than the possibility to remove the disease.

Even those who ask to be freed from hyperpigmentation or wrinkles are not always inspired by narcissistic or hedonistic feelings. Let's think about the strong reorganization of society in particular in connection with the speed and frequency of communications.

The opportunities for interaction between different people are getting more and more as frequent as fleeting.

It seems quite clear that the importance of "being good", "all right", in order to give a good impression since the first contacts or encounters is no longer evaluated with the traditional rules.

In fact in recent years, the activities connected to clothing or fashion and those addressed to the personal care, are getting significantly increased.

Obviously it needs that young doctor's get close seriously and professionally to this field without missing that the essential knowledge of techniques and procedures has to be combined with the essential experience.

So many times we can observe on one hand terrible results or damages, fortunately not so often, and on the other hand unsatisfactory or irrelevant results much more frequent.

All the procedures described in the book, which are the results of authors' experience, are able to give readers useful information about the selection criteria and the execution of it in order to optimize the possibility to get the best that these procedures can offer.

**Luigi Rusciani**

Professor of Dermatology

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# About Editor(s)

Giuseppe Curinga currently serves on the “Maddalena Hospital” in Palermo, (Oncoplastic Breast Surgery and Plastic and Reconstructive Surgery), and “Venuslab” Plastic Surgery and Laser Center in Palermo.

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He obtained the Ph.D. degree at the Catholic University of the Sacred Heart in Rome in 2007.

In 2001 and 2002 he spent two year around Europe and US (Paris, Bonn, Frankfurt, Indianapolis) to improve his skills in Dermatologic Surgery, Mohs Surgery, Liposuction).

Hi is author of more than 100 articles on topics such as dermatologic surgery, lasers, plastic and reconstructive surgery.

Dr. Rusciani lives in Rome with his wife. They are the parents of three sons.

# Forewords

In last twenty years daily practice of plastic surgeons dramatically changed, these changes can be seen especially in the field of facial plastic surgery, in fact just thinking about the so called “chemical forehead lift”, performed with botulinum toxin injections, that blurred the forehead surgical lift done with a bicoronal approach we can clearly understand how minimally invasive procedures are much more required and well tolerated by the patients nowadays. “**Minimally invasive procedures for facial rejuvenation**” edited by Dr Curinga looks as a practical guide for all the plastic surgeons, easy to be read, clear in each topic faced, it is useful for beginners in this field that needs to augment their knowledge, but in the same time it is also very useful for advanced plastic surgeons that wants to compare what they do daily in their office.

Thanks to the experience of Dr. Curinga and all the authors in the field of facial plastic surgery this is a book that can’t be missed by all the plastic surgeons.

**Raffaele Rauso**

# Acknowledgement

In addition to my gratitude to my wife, my mam, and all my family, who for many months found me constantly occupied in working on this manuscript, I would like to acknowledge and thank those teachers, colleagues and friends who helped me along the path of personal and professional development. Grateful acknowledgement is given to the co-editor Antonio Rusciani whose time and expertise made this eBook possible.

I also want to express my gratitude to my mentors at the Skinlaser Center in Rome, and particularly Prof. Luigi Rusciani, Paola Nardi and all the staff.

I am grateful to the OMICS publishing staff for their support and cooperation.

Finally, my humble appreciation goes to the contributors to this book, all very accomplished and very busy surgeons, dermatologists, and anesthesiologists, who were very gracious to dedicate their time to making this book a reality. It is now the comprehensive ebook in minimally invasive procedures for facial rejuvenation.


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## Chapter 1

# Anatomy and the Aging Process of the Face

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## Abstract

Skin aging is a complex and progressive biological process linked to the passage of time. Many of the clinical facial manifestations, influenced by aging, are caused by decrease in collagen, atrophy, loss of volume, gravity, reduction skin elasticity, gradual bone resorption, redistribution of subcutaneous tissues which result in dry and wrinkled skin that is easily bruised. Photoaging also causes telangiectasias, comedones, sebaceous gland hyperplasia, leathery skin, pigmentary changes as sunspots and lentigines. These factors are responsible of structural and physiological alterations in each skin layer that cause especially on the sun-exposed skin areas changes appearance. In an attempt to eliminate these blemishes many of aesthetic procedures, applied on the face, are often not optimal and don't ensure a natural look because they are applied without considering the anatomy and the processes of skin aging. In this chapter we analyze the anatomy of the face and the main factors that cause skin aging. It arises from two basic processes: intrinsic aging (influenced by genetics factors, cellular metabolism, hormone and metabolic processes) and extrinsic aging caused by chronic light exposure, pollution, ionizing radiation, chemicals, and toxins.

**Keywords:** Collagen; Epidermis; Elastic Fibers; Elastosis; Extrinsic Aging; Facial muscles; Facial Nerve; Free Radicals; Glycosaminoglycans; Hyaluronic Acid; Intrinsic Aging; Laxity; Metalloproteinase; Oxidative Stress; Proteoglycans; Pigmentary Changes; Skin Anatomy; Trigeminal Nerve; Ultraviolet Rays; Wrinkles

## Introduction

Skin aging is a complex biological process that arises from two basic processes: intrinsic aging (influenced by genetics factors, cellular metabolism, hormone and metabolic processes) and extrinsic aging caused by chronic light exposure, pollution, ionizing radiation, chemicals, toxins.

These factors are responsible of structural and physiological alterations in each skin layer that cause especially on the sun-exposed skin areas changes appearance. Many of the clinical facial manifestations, influenced by intrinsic aging, are caused by decrease in collagen, atrophy, loss of volume, gravity, reduction skin elasticity, gradual bone resorption, which result in dry and wrinkled skin. The presence of telangiectasias, leathery skin, pigmentary changes (freckles, sunspots, lentigines) is due instead to photoaging.

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In an attempt to eliminate these blemishes the face is often subjected to many different treatments but the aesthetic results of these procedures are sometimes not optimal and don't ensure a natural look because the various techniques are applied often without a clear understanding of the anatomy and physiological processes of skin aging.

## Aging of the Face

Aging is a multisystem degenerative process that involves the skin and the skin support systems including the bone, cartilage and subcutaneous compartments [1].

The human skin, like all other organs, undergoes chronological aging that starts from the third decade of life. The skin aging is the sum of the interactions between individual genome's expression and the environmental alterations that happen during the life.

Intrinsic aging called also chronological aging is observed in sun-protected skin of elderly persons.

Photoaging is a premature and accelerated aging process in chronically photodamaged skin. This depends primarily on degree of sun exposure and skin pigment.

One of the main pathogenetic mechanisms responsible for the process of aging skin is related to the changes induced by free radicals.

Human skin is constantly exposed to the air, solar radiation, other environmental pollutants, or other mechanical and chemical insults, which are capable of inducing the generation of free radicals as well as Reactive Oxygen Species (ROS) of our own metabolism as such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite.

Radicals can also be classified as either endogenous (generated through normal cellular processes or created by immune cells specifically to destroy pathogens) or exogenous (generated from pollution, radiation, smoking, pesticides, ionizing radiation, alcohol intake, poor nutrition, overeating etc.) As one ages, the protective antioxidants found in the different layers of the skin are greatly reduced, leading to pathological effects in the upper and lower layers of the skin.

## Extrinsic Aging or Photoaging

Photoaging is a term coined by Kligman in 1986 to describe changes that develop after many years of cutaneous exposure to UV radiation [2].

The factors responsible for extrinsic damage of skin are physical and chemical acting from the outside that induce generation of ROS and consequently oxidative stress. Ultraviolet Rays (UVR) contributes up to 80% in development of skin cancer and skin aging.

The remaining 20% is represented by other factors as cigarette smoking, nicotine gravity and the lifestyle as facial expressions, sleeping positions [1], alcohol intake, poor nutrition and overeating [3].

Individuals who have outdoor lifestyles with prolonged, unprotected and repeated exposure to UV radiation, that live in sunny climates and are lightly pigmented will experience the greatest degree of photoaging.

Photoaging is directly correlated to the quantity of UV rays received during the course of lifetime. The effects of photodamage are often evident many years before intrinsic aging is apparent.

DNA damages are repaired by specific cellular mechanism. When however, the frequency of these insults exceeds the capacity of cellular repair, the process of cellular toxicity and aging involve and consequently the risk of tumor formation [3].

Ultraviolet irradiation activates the up-regulation of MMP 1, MMP 3, MMP 9 inducing cleavage of fibrillar collagen at the level of central triple helix and consequently degradation of this [4]. In absence of perfect repair, fragments of collagen are expected to accumulate with continue UV exposure. In dermal fibroblasts is observed synthesis reduction of an important component into the dermal ECM, Hyaluronic Acid (HA). Photoaging of the skin also affects the phenotype of embedded cells such as keratinocytes, fibroblasts and dendritic cells [5].

Histologically, there are thickened basement membrane, reduction in dermal fibrillar collagen, degeneration of elastic fibers and inflammation with cell chemo attractant of inflammatory cells as degranulated mast cells, macrophages and lymphocytes. Blood vessels are dilated and slightly supported by reduced collagen. In photoaged skin, there is a paradoxical increase in glycosaminoglycans that are deposited on the abnormal elastotic material rather than in the papillary dermis. Similarly, altered elastic fibers are accumulated in the dermis, condition called solar elastosis [6].The photoaging is characterized by hypertrophy as defence mechanism against UV damage that, sometimes, over the years, can develop into benign and malignant neoplasms [7] as, respectively, seborrheic and actinic keratosis. In skin with long-term sun exposure, the melanocyte density is very high and these cells are irregular with pockets of increased and decreased numbers.

## Intrinsic Aging

Intrinsic aging called also chronological aging is observed in sun-protected skin of elderly persons. It's the consequence of natural and irreversible process of change that affects the body and entering into the skin.

The chronological skin aging is a slow and inexorable development that begins at the age of thirty years until the senescence. The factors responsible for this physiological process are:

### Ethnicity

The correlation between skin aging and ethnicity is related to the differences of pigmentation in populations [7]. The pigmentation's presence induces higher levels of sun protection accompanied by a reduction of photoaging damages.

### Anatomic

Intrinsic aging, although it is a process genetically determined and unchangeable, shows considerable variability of expression both within breeds or populations in both anatomic sites even in the same individual [7].

### Lifestyle

Cigarette smoking can accelerate aging [1]. The underlying mechanism is not well known, but elastic fibres of the dermis seem to be the major target of smoke-derived components [7,8].

### Hormonal variations

The human skin is an endocrine tissue able to synthesize hormones by itself [9].

The predominant role, played by sex hormones, is expressed in maintaining the barrier function and homeostasis of the skin.

The hormonal changes acting in the course of life are linked to gradual and fluctuating falling of circulating hormones, caused by reduced secretion of the pituitary, adrenal glands and gonads in both sex.

Physiologically, the balance between serum estrogen and androgen levels is a normal feature of human aging. In fact, the dermal metabolism of these hormones is age dependently modified [9]. With advancing age and with the achievement of menopause and andropause, the temporary and relative increase in the levels of androgen associated to estrogen's deficiency lead to important variations about internal organs and skin. Sex hormones act their functions through specific receptors localized in target organs, as skin and in particular sebaceous gland and hair follicle, where they are fundamental for the growth and differentiation; epidermal barrier ensuring homeostasis and wound healing.

The skin changes occurring with age are inexorably related to blood levels of sex hormones that can affect not only the morphology but also key functions of the skin and its appendages [7]. They regulate the production and degradation of extracellular matrix, increasing procollagen synthesis throught dermal fibroblast collagen production and inhibiting activation of Matrix Metalloproteinases (MMP).

With age, the skin undergoes gradual and significant changes, however, accentuated by photoaging factors. It's possible observe reduction of the lipids in stratum corneum and profound abnormality in cholesterol synthesis. Consequently, skin becomes more permeable and more susceptible to mechanical injury and infectious diseases. The sebaceous gland cells begin to shrink in the size but not in the number that remain the same. This condition about the aging of sebaceous glands is reflected in a progressive decrease in synthesis and secretion of lipid and sebum with cutaneous xerosis induced [9,10].

Intrinsic ageing of the skin is a slow process, which causes changes in tissue structure.

The thinning of the epidermis and the structural destruction of dermal collagen fibers (particularly in the reticular dermis) induce the appearance of finely wrinkles with exaggeration of facial expression lines, laxity, and pallor [1,11].

Epidermal and dermal atrophy exhibits reduced numbers of mast cells and fibroblasts [8,6].

Into reticular dermis, the elastic network is irregularly thickened and fragmented and there is loss in glycosaminoglycans that is characteristic of intrinsically aged skin compared to photoaged skin [11]. Chronological skin aging is expressed in loss of extracellular matrix and hyaluronate that is the first important component able to stabilizing intracellular structures [1]. These conditions induce structural and functional decline of the skin (Table 1).

| Photoaging | Chronologic Aging |
|---|---|
| Xerosis | Xerosis |
| Telangiectasia | Thin Skin |
| Premalignant lesions | Fine Wrinkles |
| Sebaceous gland hyperplasia | Loss Of Underlying Fat |
| Leathery skin | Reduction In Bone Mass |
| Pigmentary changes | Sagging Skin |
| Deep wrinkling | Pigmentary changes |
| Laxity | |
| Atrophy | |
| Elastosis | |

**Table 1:** Clinical features of photoaging and chronological aging.

## Clinical Signs of Aging

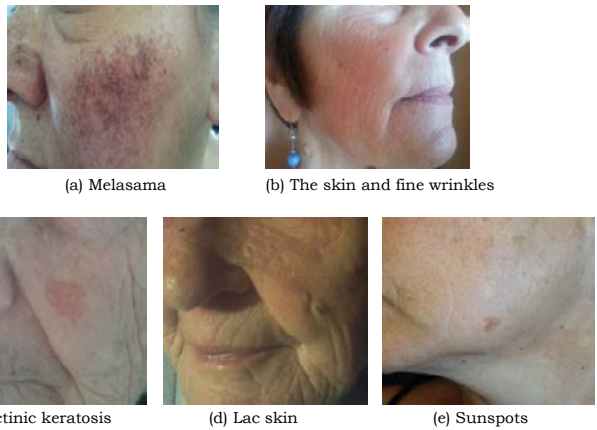
Many of the clinical facial manifestations arise from combined and simultaneous effects of atrophy, loss of volume, gravity, reduction skin elasticity, gradual bone resorption, redistribution of subcutaneous tissues.

Compared with the cute young, in the senescence the face is gaunt particularly at the temples and cheeks because of reduction muscle mass and cutaneous fat, the lips are thinned and volume loss interesting the eyes beginning at the level of tears troughs [1].

The skin, soft tissues (subcutaneous fat, muscle and fascia) and bone support are individually affected by, but they also act simultaneously to determine the phenotypic structuring of the face [12,13,14].

Clinically, the photoaging is characterized by xerosis, telangiectasias, comedones, sebaceous gland hyperplasia, leathery skin, pigmentary changes (freckles, melasma, sunspots, lentigines) and deep wrinkling, laxity, loss of tensile strength. Repetitive facial movements actually lead to fine lines and wrinkles. The Glogau classification system was developed to objectively measure the severity of photoaging and especially wrinkles.

The clinical signs of intrinsic aging are not usually evident until old age when the surface appears pale and characterized by xerosis, thin skin, fine wrinkles, loss of underlying fat, reduction in bone mass that cause sagging skin (Table 1). Intrinsic aging is also characterized by alterations in skin pigmentation that lead to the appearance of evident telangiectasias, lentigines, melasma and to clinical aspects of poikiloderma [1] (Figure 1).



(a) Melasama (b) The skin and fine wrinkles

(c) Actinic keratosis (d) Lac skin (e) Sunspots

**Figure 1:** Clinical signs associated with intrinsic aging and photo-aging.

## Upper third (forehead and brows)

The skin aging process leads to a gradual loss of subcutaneous volume at the level of forehead, temples, brow and upper eyelid [12]. The volume lost is not a deficit of fat or collagen but rather a inter-correlation between fat atrophy, thinning of collagen and bone resorption [15].

This condition accentuates the underlying anatomic structures. Forehead and supraorbital rims are objectively more pronounced as well as the muscles of the brow. The loss of fullness in the upper eyelid induces brow and eyebrow ptosis descending to the superior orbital rim, according to the force of gravity. Intraorbital fat causes accentuation of orbital septum and the intrinsic tone of the glabellar, procerus and frontalis muscles gives rise to increase in the depth of wrinkles [12] (Figure 2).

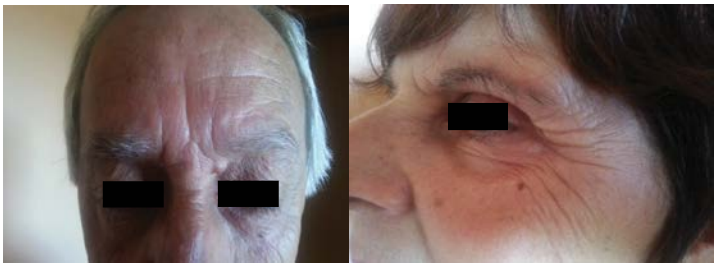


**Figure 2:** Expression wrinkles.
a) Repeated traction by facial muscles causes the formation of glabellar, procerus, and frontalis wrinkles
b) Ptosis of superior orbital rim and periocular wrinkles.

## Middle third (midface)

In the midface, the malar prominence and progressive buccal hollowing are linked to loss of subcutaneous tissues, which is expressed in a less healthy facial proportion [12].

Consequential effect manifests itself in intrinsic tone in the orbicularis oculi muscle, giving rise to "crow's feet" rhytids. These wrinkles may be static (present at rest) or dynamic (dependent on muscle movement) [15].

Depletion of subcutaneous tissue induces the development of the malar crescent over the zygomatic eminence and the nasojugal fold. In the infraorbital area, instead, this loss causes infraorbital fat pads called "palpebral bags" and accentuation of the tear-trough depression. Loss of fullness between the orbicularis oculi muscle and the overlying skin induces darker coloration resulting in a tired eye appearance, attributable to dermal melanin deposition.

The reduction of the volume of the cheeks is accompanied by that malar. The loss of fullness occurs in the glabella, nasion and upper dorsum and is also linked to alteration of the nasal cartilage.

Pyriform remodeling and upper maxillary resorption contribute to the appearance of increased nasal projection [12].

## Lower third (chin, jawline, and neck)

During the fifth and sixth decades of life, the bone loss and the depletion of malar and perioral fat deposits withdraw jaw, cheeks, leading to loss of definition of the jawline [15].

This condition is associated with descent of the mid and lower face characterized by fat pads, more or less round, which descend from the zygomatic and periorbital areas. This gravitational movement leads to the nasolabial crease.

The skin is marked by perioral rhytides (Figure 3). At the level of the buccal rhyme, upper lip to disappear while the lower lip becomes more pronounced [1].

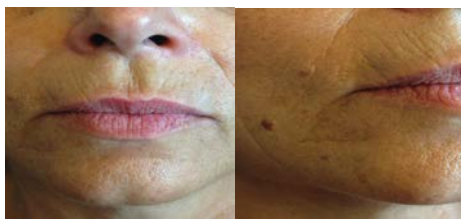


**Figure 3:** Perioral rhytides. Upper lip appears thinner while the lower lip becomes more pronounced

At the level of mandible, the angle appears to merge from the buccal region into the neck. In the chin, loss of lateral and inferior volume results in relative protrusion of the central area. All these clinical signs leads to the development of the characteristic jowled “turkey neck” deformity [12].

Therefore the face is often subjected to many different treatments but the aesthetic results of these procedures are sometimes not optimal and don’t ensure a natural look because the various techniques are applied often without a clear understanding of the anatomy and physiological processes of skin aging.

In this chapter the authors underline and confirm the importance of knowledge about face anatomy and morphological and functional changes related to aging skin.

These aspects are important in order to obtain a natural rejuvenation of the face through aesthetic surgery.

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## Chapter 2

# Anaesthesia for Cosmetic Procedures

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## Abstract

A wide range of anaesthetic procedures can be used with facial surgery. They can be categorised as:

- Locoregional anaesthesia:
  - o Topical anaesthesia: applied to mucous surfaces and to skin. Act on nerve endings.
  - o Infiltration anaesthesia: applied by subcutaneous injection. It also acts on nerve endings.
  - o Regional anaesthesia: the anaesthetic is injected at different levels, affecting several nerves.
  - o Nerve block anaesthesia: the anaesthetic is applied directly to a specific nerve.
- Conscious sedation
- Unconscious sedation
- General anaesthesia.

## Local Anaesthetics

It is important to remember that a signed informed consent form must be obtained prior to using local anaesthetics, given that adverse reactions may occur: allergies, systemic toxicity, nerve damage, and pain during and after the injection, among others. Also, make sure there is emergency equipment reachable when using local anaesthetics.

### Mechanism of action

Local anaesthetics temporarily block nerve conduction given that they affect the flow of sodium ions through the sodium channels in the nerves. This process reduces the rate of membrane depolarisation, eventually inhibiting the propagation of the axon potential through the nerve axon, with sensitivity being lost in the corresponding area of the body.

The C fibers (involved with nociception and temperature regulation) are the first to be affected, given that they are demyelinated and smaller. The motor neurons, which are usually larger and myelinated, are only partially affected by the LA doses used in clinical practice.

All local anaesthetics have a similar chemical structure. They can be split into 2 groups based on the bond between the aromatic nucleus and the hydrocarbon chain.

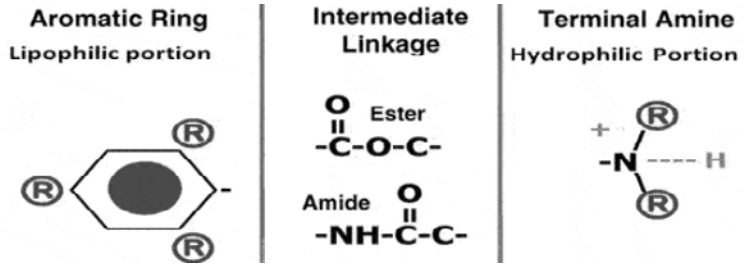


**Figure 1: Chemical structure of local anaesthetics.**

The bond (ester or amide) determines how the Local Anaesthetic (LA) is metabolised: esters (for example, procaine) are metabolised by plasma pseudocholinesterase, whilst the amides (lidocaine) are metabolised in the liver.

Local anaesthetics are weak bases. They enter the body with a physiological pH of 7.35-7.45, as a non-ionised, basic form, meaning they are lipid-soluble and can pass through the plasma membrane and start acting.

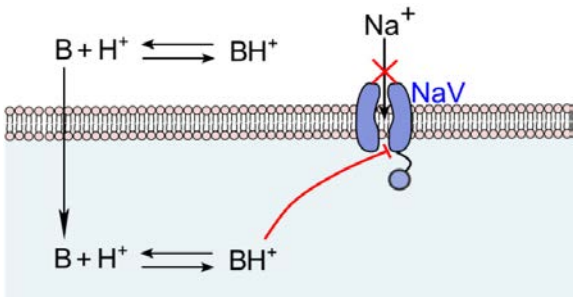


**Figure 2:** Mechanism of action of local anaesthetics.

B = Base (non-ionised fraction, lipid-soluble); BH+ = cation (ionised fraction, water soluble) [4], the blue is a voltage gated sodium channel and the ionozed

anaesthetic inhibits it in the intracellular fluid. When the influx of sodium is interrupted, an action potential cannot be arised and the signal conduction is inhibited.

They need to pass through the nerve membrane to undertake their action given that they have to bond with the receptor from the cytoplasmic side of the membrane.

The higher the pKa of the local anaesthetic (pKa: acid dissociation constant at logarithmic scale is the pH at which the ionized equals to the non-ionized), the higher the ionised fraction at physiological pH, meaning, therefore, it is more difficult to pass through the plasma membranes (for higher ionisation, higher water solubility and lower lipid-solubility, and so the anaesthetic acts more slowly). Therefore no effect can be expected in infected areas with a low pH.

## Additives to Local Anaesthetics

### Epinephrine

Offers the follow benefits:

-reduces the systemic absorption of the LA, and consequently, the toxicity

-prolongs the anaesthetic action (given that tissue clearance through systemic circulation is reduced)

-improves haemostasis, given that it reduces bleeding thanks to its vasoconstrictor effect.

Solutions containing epinephrine are more acidic because of the epinephrine preservative; the antioxidant, sodium bisulphite. This increased acidity leads to a delay in the start of the action (greater ionisation in the molecules, which are therefore more water soluble). The injection pain also increases.

No benefit is gained from using a concentration over 1:100000 (1 mg Additive in 100 ml). The maximum vasoconstrictor effect is achieved at that concentration. The effect is fully established after 7-10 minutes.

Contraindications for the use of epinephrine are: patients with unstable angina, cardiac dysrhythmia, uncontrolled hypertension, pregnant patients with placental insufficiency.

If contraindicated, a phenylephrine concentration of 1:20000 can be used, but it is not as effective as epinephrine.

It should be noted that vasoconstrictors are prohibited for digital or other acral regions (e.g. ear, tip of the nose) due to their possible ischaemic complications.

### Bicarbonate

The local anaesthetic solution becomes alkaline when added, which leads to:

-Reduced injection pain.

-Faster onset of action.

The most basic local anaesthetics, such as bupivacaine, levobupivacaine, or ropivacaine can have a tendency to become alkaline; bicarbonate should only be used with lidocaine, mepivacaine, or prilocaine.

## Local Anaesthetics

### Lidocaine

The most commonly used LA. 1% or 2% forms, with or without epinephrine. The effect lasts around 1.5 hours with epinephrine and 3 hours without epinephrine.

The maximum dose is 3 mg/kg, or 7 mg/kg if used with epinephrine. Recently published literature refers to 35 mg/kg if used with epinephrine.

### Bupivacaine

It is also widely used, given its long effectiveness (3-6 hours). The effect can last up to 10 hours if used with epinephrine. It comes in 0.25% and 0.5% forms. It has a fast onset of action, as well as long-lasting action, when combined with lidocaine, which is why it is commonly used. The maximum dose is 2.5 mg/kg, or 3 mg/kg if used with epinephrine.

## Mepivacaine

It is similar to lidocaine, but lasts a little longer (up to 3 hours) and it is a little more toxic. It comes in 1% and 2% forms. Maximum dose 5-6 mg/kg.

## Cocaine

No longer used.

## Tetracaine

Similar to cocaine. Used for nasal surgery. Also used in combination with EMLA for closed reductions of nasal fractures. Very toxic due to slow metabolism. Maximum dose of 1 mg/kg. It comes as 0.05% to 4% solutions. Effective for 1-3 hours.

## Ropivacaine

Concerns about bupivacaines toxicity led to the development of ropivacaine. Ropivacaine is an aminoamide local anaesthetic. It has been used clinically for the past decade. Clinical evidence indicates that it is indeed less toxic than bupivacaine. In particular, it is less cardiotoxic. The intensity and duration of the motor block are lower than with bupivacaine. It is slightly less potent than bupivacaine (in peripheral nerve blockade, 0.5% bupivacaine is equipotent with 0.6% ropivacaine). It has a very close clinical profile as bupivacaine but its increased safety margin gives it a clear advantage. It'll probably replace bupivacaine in the near future. It has been found that when adrenaline is added, the anaesthetic effect of ropivacaine is not prolonged, meaning there is no need to use this adjuvant treatment, and so the side effects of secondary absorption of the vasopressor agents are eliminated. Maximum dose of 3-4 mg/kg.

## Levobupivacaine

This is a relatively new agent and to all intents and purposes is the same as bupivacaine. Bupivacaine is a racemic mixture of the R and S enantiomers. Levobupivacaine contains the S enantiomer only. Compared with bupivacaine it is said to have greater vasoconstrictive action and less motor block. The real advantage is that it is apparently less cardiotoxic. It may replace bupivacaine for safety reasons but it is significantly more expensive. It is not currently licensed for subarachnoid injection.

The recommended maximum safe dose of levobupivacaine is as follows:

Levobupivacaine - 2.5-3.0 mg/kg (insufficient data).

| DRUG | LIDOCAINE | PRILOCAINE | BUPIVACAINE | LEVOBUPIVACAINE | ROPIVACAINE |
|---|---|---|---|---|---|
| **Description** | Amide | Amide | Amide | Amide | Amide |
| **Relative potency** | 2 | 2 | 8 | 8 | 6 |
| **Onset** | 5-10 min | 5-10 min | 10-15 min | 10-15 min | 10-15 min |
| **Duration without epinephrine** | 1-2 hours | 1-2 hours | 3-12 hours | 3-12 hours | 3-12 hours |
| **Duration with epinephrine** | 2-4 hours | 2-4 hours | 4-12 hours | 4-12 hours | 4-12 hours |
| **Max dose without epinephrine** | 3 mg/kg | 6 mg/kg | 2 mg/kg | 2.5 mg/kg* | 3 mg/kg* |
| **Max dose with epinephrine** | 7 mg/kg | 9 mg/kg | 2.5 mg/kg | 3 mg/kg* | 4 mg/kg* |

**Table 1:** Local anaesthetic drug information.

* Indicates probable Safe Maximum Dose (Insufficient Data).

The relative potency of the anaesthetics is referred to PROCAINE [2].

# Complications of Las

As soon as adverse effects occur, the administration of a LA must be stopped immediately and if not happened in advance an intravenous cannula must be placed and a monitoring (EKG, $O_2$ saturation,...) must be applied.

### Toxicity from local anaesthetics

Both the face and scalp contain many capillaries, meaning that LA absorption is greater than in other areas on the body, meaning that it essential to be clear on the toxic side effects derived from LAs: neurological disorders that occur prior to heart disorders: anxiety, headache, nystagmus, buzzing in the ears, a metallic taste in the mouth, numbness in part of the face.

All these symptoms end up giving rise to convulsions, apnoea, coma, and death. Treatment of all these symptoms is the same as with convulsions caused by a different aetiology: diazepam, midazolam. Heart disorders appear later, including cardiac depression, hypotension, shock, PR interval prolongation, and eventually, cardiac arrest. Bupivacaine is most toxic LA for the heart, given its affinity for the heart's calcium channels.

### Allergy to LAs

This is extremely rare among the amides. Given that they metabolise into PABA due to the action of pseudocholinesterases, esters produce stronger allergic reactions.

# Topical Anaesthesia

- EMLA (Eutectic Mixture of Local Anesthetics)

o A cream containing 2.5% lidocaine + 2.5% prilocaine. Once applied, it should be covered with a dressing of some description to ensure effectiveness. It produces a topical anaesthetic effect for 45-60 minutes after application.

| Product | Active Ingredient | Time to Onset | Duration of Action | Common Adverse Effects |
|---|---|---|---|---|
| **EMLA** | 2.5% prilocaine/ 2.5% lidocaine | 45-60 min | 4 h | Blanching, erythema |
| **LMX-4** | 4% liposomal lidocaine | 20-30 min | 1 h | Blanching, erythema |
| **Gebauer's Pain Ease** | Ethyl chloride | Immediate | 15 sec | Temporary alteration of skin pigmentation; vasoconstriction can increase difficulty of venous access |
| **Synera** | 70 mg lidocaine/ 70 mg tetracaine | 20-30 min | 3 h | Erythema, blanching, edema |
| **J-Tip** | Not supplied with active ingredient | Specific to active ingredient | Specific to active ingredient | "Popping" noise upon administration may frighten some children |
| **Zingo** | 2.5 g sterile lidocaine powder | 1 min | 1 h | Erythema, petechia, edema |

**Table 2:** Topical anaesthetics.Min: Minute; Sec: Second; Source: US Pharm

# Facial Locoregional Anaesthesia

### Anatomy

Facial sensitivity comes from the fifth cranial nerve (trigeminal) and other nerves from the cervical plexus. The trigeminal nerve splits into 3 branches [3].

- V1: ophthalmic nerve

- The main branch, the supraorbital nerve
- Supratrochlear
- Infratrochlear
- Nasociliary
- V2: maxillary nerve
- Zygomatic nerve
  - Zygomatic temporal
  - Zygomatic facial
- V3: mandibular branch
- Sublingual nerve
- Mental
- Buccal
- Lingual
- Cervical plexus

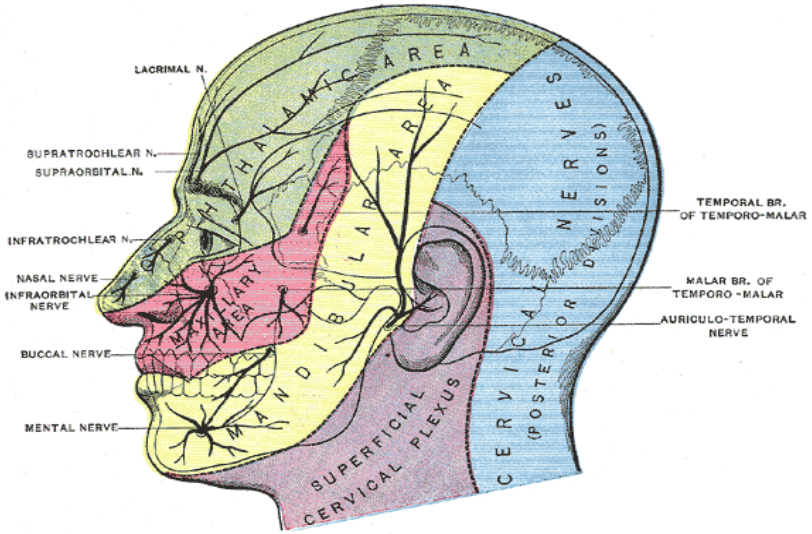


**Figure 3:** Grays's anatomy of the human body [3].

1. Ophthalmic Nerve

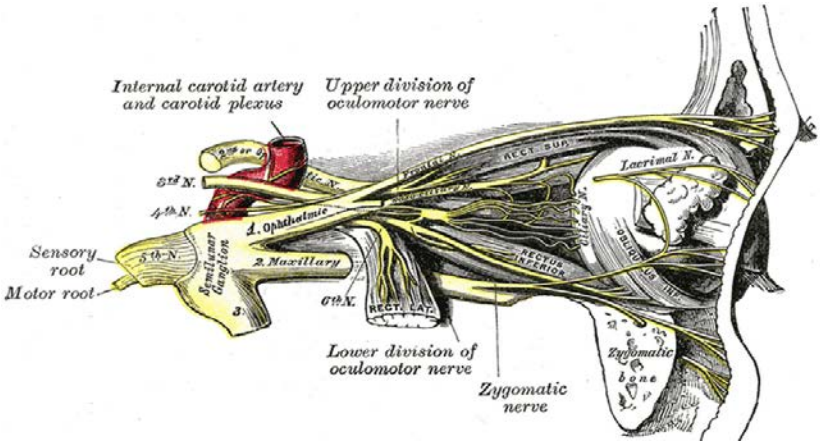


**Figure 4:** Grays's anatomy of the human body [3].

2. Maxilliary Nerve

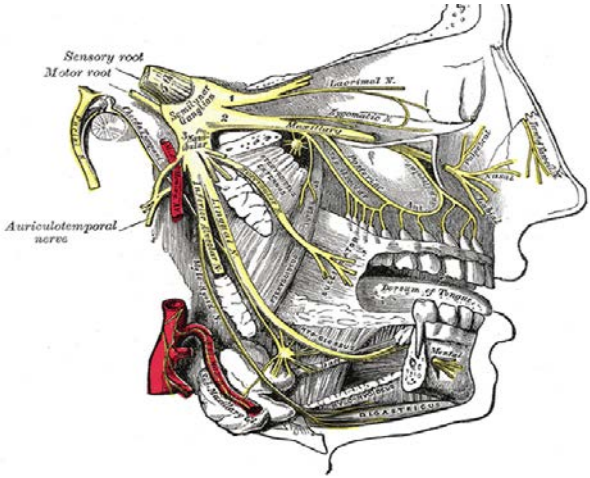


**Figure 5:** Grays's anatomy of the human body [3].

3. Mandibular Nerve

Following, the previously indicated doses: local infiltration of lidocaine provides 1 to 2 hours of analgesia, which can be extended to 2 to 4 hours with the addition of epinephrine. The maximum dose for plain lidocaine is 4.5 mg/kg (up to 300 mg total). For lidocaine with epinephrine, the dose increases up to 7 mg/kg (500 mg total). In practical terms, for a 70 kg patient, that translates into 30 mL of 1% plain lidocaine, or 50 mL of 1% lidocaine with epinephrine. Bupivacaine provides 4 to 8 hours of analgesia; the addition of epinephrine increases the duration to 8 to 16 hours of relief.

1. When bupivacaine is used, a concentration of 0.25% is typical, with a 2.5 mg/kg safety limit in adults and a 2 mg/kg safety limit in children.
2. For large or multiple wounds, the total amount of anaesthetic required if using local infiltration can exceed safe limits and lead to toxicity, making the use of nerve blocks essential.

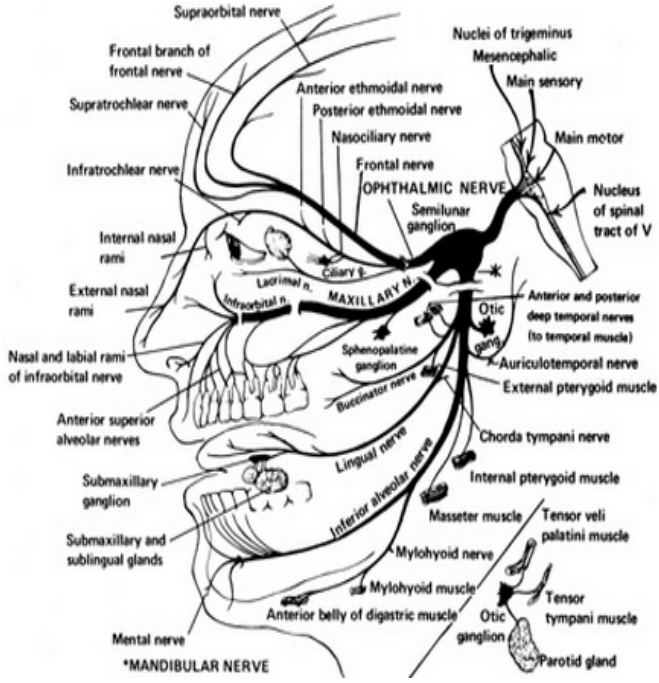


**Figure 6:** Grays's anatomy of the human body [3].

1. Ophthalmic Nerve Block

- Material: 3 cm 25G needle
- Supratrochlear block: injection in the join between the nose and the supraorbital ridge. Spread of injections.

**Figure 7**

Supraorbital block: The supraorbital opening is located in the middle of the supraorbital ridge. The needle is inserted below the aforementioned opening and a spread of injections are undertaken. 3-4 ml of anaesthetic.

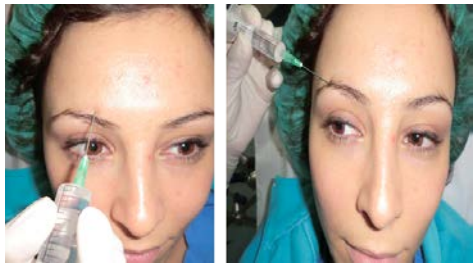

**Figure 8: Tear duct block:** Inject above the eyebrow.

2. Maxilliary Nerve Block

- Very difficult access requiring consultation. The branch ending, the infraorbital nerve, can be accessed: it is on a line between the pupil and the corner of the mouth. It is located 1 cm below the lower edge of the orbit. Inject 2-3 ml of LA. Paraesthesia can occur.

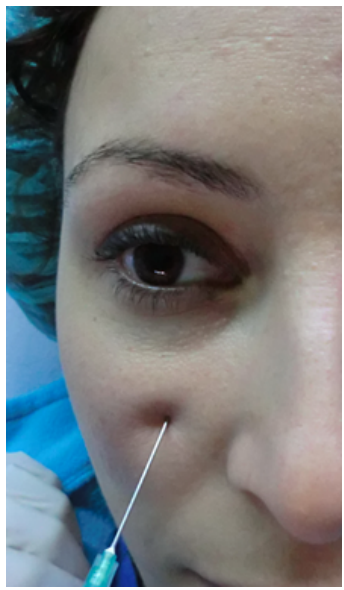

**Figure 9**

3. Mandibular Nerve Block

- Access is very difficult in a non-hospital setting. However, its branch ending, the mental nerve, can easily be blocked at its ending though the mental opening, 1-2 cm under the corner of the mouth. 2-3 ml of local anaesthetic [4].

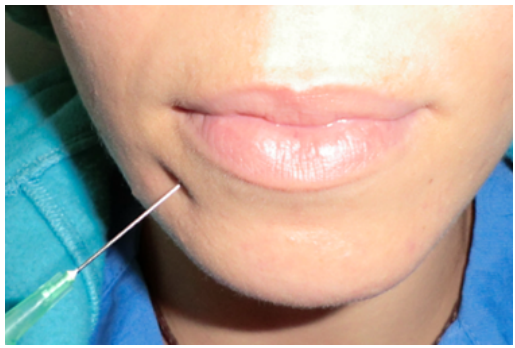

**Figure 10**

## Nasal Anaesthesia

This involves anaesthetising the infraorbital nerve for the lower lateral regions of the nose and the supratrochlear nerve for the upper lateral regions. For the middle distal areas of the nose, a dorsal nasal nerve block is required: feel for the transition between the nasal bones and the cartilage. Inject 1-2 ml at that point [5].

### Pinna

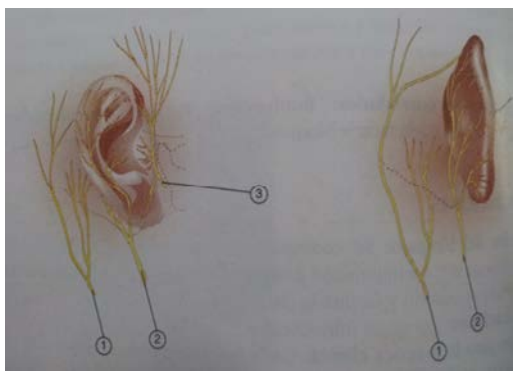


**Figure 11**

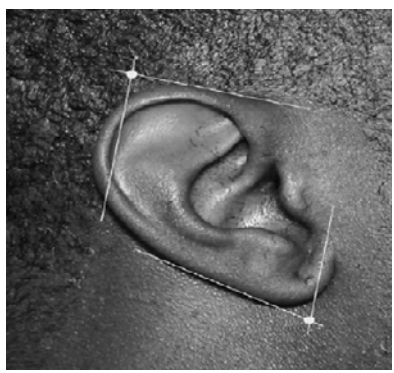

**Figure 12:** Ear ring block.

A ring block around the ear: the V technique: insert the needle in the pre and retroauricular areas, converging in the lower region. Administer the anaesthetic as the needle is being withdrawn.

### Area to the rear of the pinna

The innervation of this region comes from the lesser occipital nerve and the great auricular nerve. After previously separating the pinna, inject 3-4 ml whilst the needle moves through the posterior sulcus.

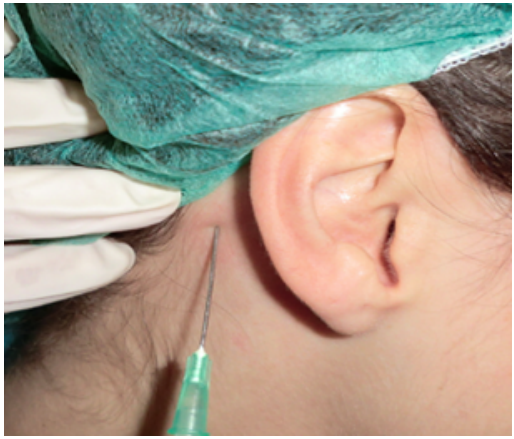

**Figure 13**

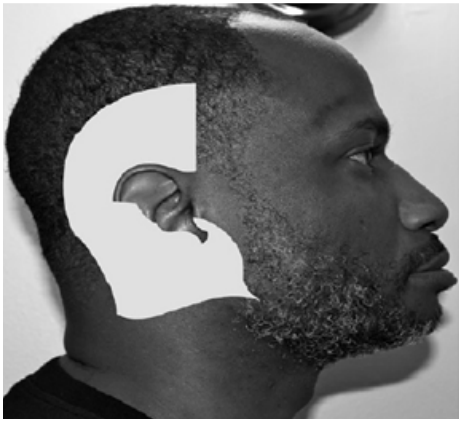

**Figure 14:** Greater auricular and lesser occipital nerve distribution.

(Courtesy of Alisa Gibson, MD, DMD. University of Maryland School of Medicine, Baltimore, MD.)

## Regional Block of the Scalp

### Indication

Anaesthesia of the scalp down to the periosteum.

## Technique

The scalp is innervated by branches of the trigeminal and cervical nerves. These nerves can be anesthetized as they penetrate the scalp. They become subfascial along a line that encircles the head (like a skull-cap). This line passes just above the tragus and through the glabella and occiput. A wheal should be raised in the subdermal plane along this line. About 10 ml of lidocaine is required every few centimetres.

## Surgery under conscious sedation

Depressed level of consciousness to the point that the patient is in a state of relaxation, but maintains respiratory drive and the ability to protect the airway. The patient is also capable of purposefully responding to physical and verbal stimulation. This is in contrast to deep sedation, in which the patient is unable to respond to verbal stimuli, will only respond to painful stimulation with withdrawal and has potential compromise of airway protection and respiratory drive. As opposed to Monitored Anaesthesia Care (MAC), in which an anaesthesiologist or nurse anaesthetist are required, conscious sedation can be performed by a nurse under the supervision of the operating surgeon almost all aesthetic procedures can be performed using a local anaesthetic combined with some form of intravenous sedation. These include breast augmentation, breast reduction, mastopexy, abdominoplasty, rhytidectomy, rhinoplasty, blepharoplasty and liposuction.

Benefits to the use of conscious sedation:

1. The complications associated directly with the administration of a general anaesthetic are avoided. These are not negligible, and include adverse cardiopulmonary effects, airway injury and positional nerve injuries. Such complications occur in roughly 1-2% of aesthetic procedures performed under general anaesthesia.
2. The incidence of postoperative nausea and vomiting, which account for most unintended admissions after outpatient surgery, is much less than that associated with general anaesthesia most patients have no memory of the procedure, no recollection of experiencing pain, and many choose to undergo conscious sedation at subsequent procedures. Because it can be performed safely without the presence of an anaesthesiologist, there is a considerable saving in cost to the patient

Issues when used with conscious sedation:

1. Sedation requires a surgeon who can “multi-task,” focusing on the operation as well as on the vital signs and level of arousal of the patient
2. The patient is conscious and can shift position or move freely, necessitates that the surgeon be prepared to stop working at any moment
3. No anaesthesia present, meaning that if a major complication occurs, the surgeon needs to be able to resolve it: such as an allergic reaction, pain, vasovagal response, etc.

## Preoperative considerations

Prior to using conscious sedation for the first time, the surgeon must have extensive experience with the medications he will be using, as well as their side effects and reversal agents. He must also be familiar with ACLS (Advanced Cardiac Life Support) protocol, airway management and have readily available resuscitation equipment. Immediate access to an anaesthesiologist in case of emergency is strongly recommended.

Only use with ASA 1,2. Also on patients suffering significant anxiety about the operating room that cannot tolerate conscious sedation [6].

Procedure: Prior to the procedure, patients may benefit from premedication with intravenous diazepam (Valium), administered in increments of 5-10 mg. The dose administered usually ranges from 10 to 50 mg, with the goal being adequate preoperative subjective relaxation of the patient with the desired endpoint being of slurred speech. Oral diazepam is also an option; however, it has to be given almost an hour prior to the procedure in order to be effective. A second medication that should be administered preoperatively is an antiemetic. Ondansetron (Zofran), given as a single 4 mg intravenous injection is used routinely at our institution. Recently, we have found that clonidine (0.1-0.3 mg PO) given 30 minutes prior to the procedure is not only effective in lowering blood pressure during surgery; it also contributes significantly to patient relaxation during the procedure. It does, however, cause post-procedure orthostatic hypotension.

**Intravenous sedation regimens**

1) Combined use of midazolam and fentanyl. Midazolam has both anxiolytic and amnestic effects, whereas fentanyl is a potent, short-acting analgesic. The combination of fentanyl and midazolam is superior to midazolam alone in decreasing patients' subjective report of pain and anxiety. The main drawback of fentanyl is respiratory depression; however unlike other commonly used intravenous opiates such as morphine, it does have a very short half-life. Midazolam, in contrast, has minimal effects on the respiratory system except in the elderly, in which lower doses should be utilized. Both of these medications have antagonists. Flumazenil and naloxone the antagonists of midazolam and fentanyl respectively, should be readily available in the operating room.

2) Another method of intravenous sedation involves the use of propofol in combination with an opiate and benzodiazepine. The fact that a deeper level of sedation can be maintained makes this technique preferable for selected patients who are very anxious. Nevertheless, the disadvantage of this combination is the higher risk of respiratory depression, and the lack of a reversal agent for propofol. This technique necessitates a higher degree of experience and training in anaesthetic technique including the ability to intubate the patient if needed.

One nurse should be responsible for continuously monitoring patient status using pulse oximetry, blood pressure and cardiac monitoring.

Based on the patient's condition, 0.5 to 2 mg of midazolam should be administered at the 5 minute intervals. In addition, fentanyl should be given in increments of 12.5 to 50 mcg. After local anaesthetic is infiltrated, fentanyl administration is infrequently required, except in preparation for subsequent local anaesthetic administration to a new surgical site. The total dose of fentanyl should rarely exceeded 200 mcg over the course of the procedure. Toward the end of the case, the amount of sedation should be decreased to allow the patient to slowly return to a normal state of arousal and awareness.

The ability of the patient to maintain oxygen saturation over 95% without supple- mental oxygen is a useful guideline to avoid over sedation (crossing from conscious to deep sedation). Occasional periods of deep sedation may occur, usually lasting for a few minutes at most. Brief stimulation and jaw thrust may be required to maintain adequate ventilation. As a safety measure, the capability to convert to general anaesthesia or immediate assistance from an anaesthesiologist should always be available.

Following the procedure, many hospitals will allow patients to bypass the recovery room and proceed directly to the outpatient day surgery area. This saves the patient the extra costs of recovery room care. Patients are monitored postoperatively in a standard manner.

Those who choose to go home the day of surgery must meet criteria for discharge (ability to ambulate to a chair and the bathroom, bladder control, tolerate oral intake without emesis). Patients who received preoperative clonidine must be monitored for orthostatic hypotension.

Inpatient stay in an observation unit is appropriate for longer cases that involve multiple procedures, as well as for older patients who live alone.

In very rare instances, a patient may require jaw thrust, mask ventilation or narcotic reversal. It is critical that the surgeon be comfortable performing these steps if necessary.

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## Chapter 3

# Photographic Documentation and Informed Consent

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## Abstract

The first part of the chapter is focused on the critical points and guidelines about photographic documentation in plastic surgery. Uses of photographic documentation include documentation for medical records, insurance companies, legal needs, preoperative planning, intra-operative reference, surgeon self-assessment, sharing results with colleagues, patient communication, presentations and publications. So, clinical photography, particularly if high-quality photography, is a critical component of the practice of facial plastic surgery. Whoever is designated to do the photography must appreciate the importance of consistent camera settings, careful patient positioning, knowing the correct views to obtain for specific procedures. The critical points then to consider in taking medical photographic documentation are the setting of the medical portrait studio, the choice of camera and lenses, the choice of the light, the patient's preparation and standardization of the specific criteria according to the anatomic area, the image storage and consent for photo documentation. Implementation of the simple general and specific criteria proposed allows reasonable standardization of image capturing on behalf of personnel with no particular proficiency in photography.

The second part of the chapter is focused on the critical points and guidelines that can help the physician to obtain a valid informed consent. The informed consent represents the framework of the whole medical practice both from the juridical and from the ethical point of view. The roots of modern medical informed consent go back to 1914 when a New York judge stated that self-determination came to be the primary justification for legal requirements of attainment of consent from the patients. The informed consent process, an integral part of modern health service delivery, takes on special importance in aesthetic medicine. Although cosmetic procedures have lower risks of catastrophic outcomes than many other types of surgery, the informed consent process that surrounds it has "supercharged" elements. High expectations and low tolerance for risk on the patient side meet competitive market pressures on the provider side and complexes.

Minimally Invasive Procedures for Facial Rejuvenation
Edited by: Giuseppe Curinga and Antonio Rusciani

# Photographic Documentation

## Introduction

"A picture is worth a thousand words". This adage is particularly true in plastic surgery and, for our aim, in facial plastic surgery. In fact, photographic documentation in facial plastic surgery is essential both for the surgeon and patient, both for clinical and scientific purposes.

Uses of photographic documentation include documentation for medical records, insurance companies, legal needs, preoperative planning, intra-operative reference, surgeon self-assessment, sharing results with colleagues, patient communication, presentations and publications. So, clinical photography, particularly if high-quality photography, is a critical component of the practice of facial plastic surgery.

Surgical planning and assessment of successful outcomes would be impossible without use of consistent and accurate photo documentation. Preoperative photographs assist in surgical planning and allow for effective communication of patients' perceptions and wishes. Comparison of preoperative and postoperative photographs allows surgeons and patients to accurately evaluate the outcome of the procedure. Review of photographic outcomes provides a surgeon with an opportunity for self-assessment and modification of surgical techniques.

If photography is part of recent past, medical photography has existed for nearly 150 years. In 1840, the first medical images were produced by Alfred Donne with a microscope-daguerreotype.

The first surgeon to use preoperative photography was Gurdon Buck in 1845, with orthopedic surgeon Berhend following shortly thereafter, capturing pre- and postoperative pictures of his patients.

The first recognized medical documentation of a reconstructive procedure was in 1863, with 7 pictures demonstrating a 2-stage nasal reconstruction by Balossa [1]. The importance of medical photography was recognized early on by one of the pioneers of plastic surgery, Sir Harold Gillies, who gave a speech at the first International Congress of Plastic Surgery in 1955 and claimed photography was one of the most important advances in plastic surgery [2].

For facial analysis, Holly Broadbent [3] described one of the earliest standardized techniques. He detailed a method for taking consistent radiographs to obtain craniofacial measurements, known as cephalometry. Skeletal landmarks, measurements and relationships were defined. Skeletal and soft tissue cephalometric analysis is still a useful tool for pre-surgical planning in orthodontic and orthognathic treatment.

Another approach to facial analysis was described by Bahman Guyuron who used life-size photographs for soft tissue cephalometric analysis. During patient photography, he placed a removable marker on the patient to allow for a precise, full-scale, life-size photo-

graph enlargement. Using drafting film overlying the photographs, Guyuron described a series of steps of drawn lines, measurements, and angles to critically analyze the patient's frontal and lateral views for surgical planning of a rhinoplasty [4]. By using soft tissue landmarks on the life-size photographs, he added that surgeons, who were not so artistically inclined nor had a keen eye for aesthetics, would be able to carefully analyze and predictably obtain optimal aesthetic outcomes.

Thus, whether using radiographs or photographs, guidelines were established for the ideal aesthetic facial proportions, which facilitated accurate facial analysis. Surgeons were then able to strike a balance between their artistry and their technical skill by objectively measured data points or analyses.

Besant-Matthews suggests the idea of surgeons serving as "functional photographers," a term he designates for someone at a level between a professional and an amateur. He states that functional photographers, while not dependent on pictures as a career, use photography as an essential element of their occupation [5]. By expanding his knowledge of photography, lighting, and medical portrait studio setup, the facial plastic surgeon can obtain more consistent and higher quality images.

Good-quality photographs are therefore important. Several factors contribute to quality, such as the appropriate setting and background, standardization of subject position, and the type of flash; however, none of these factors can be effective without a good camera and lens.

Photographic standardization according to well-established criteria is required to obtain significant and comparable images. Photographic standards in plastic surgery have already been highlighted in various articles [6,7].

Unfortunately, technical photographic guidelines oftentimes require advanced skills not common among nonprofessional photographers. A plastic surgeon's everyday activities involve taking consistent and valid photographs despite technical and environmental limits. Although standardization is easy if surgeons have the advantage of a photographic studio setup, image capture on a ward or in an outpatient clinic is not as consistent in terms of photographic standards.

Technological advances have allowed digital images to be archived and morphed with computer imaging software, which has led to the advanced capability for performing objective facial photograph analysis using imaging software.

The prominent role of photography in facial cosmetic and reconstructive surgery places significant importance on using precisely defined standards during photo-documentation to achieve consistent and reproducible results.

Deviations from standardization can lead to misleading results. A study by Daniel and colleagues [8] illustrated that small changes in positioning of lights can change the appearance of nasal tip anatomy in photographs without surgery. These investigators showed that on decreasing the angle between the subject-camera axis and the lighting, the tip defining points (and light reflexes in the eyes) appear closer together. Daniel and colleagues coined the term "photographic tip rhinoplasty" to describe this phenomenon when lighting is changed. More recently, Sommer and Mendelsohn [9] found that small changes in patient positioning such as neck extension and jaw protrusion led the majority of blinded judges to believe that the patients underwent successful facelift and neck liposuction. The slight change in positions gave the appearance of a more refined.

Standardization is required also in color's setting to value the effect of dermatologic treatments. In order to provide objective, quantitative color information in skin lesions, devices such as reflectance spectrophotometer and reflectance colorimeter have been successfully

used during the past decade, though they are too expensive and technically complex to be handled in routine clinical situations. Reflectance skin color measurements require direct contact of the probe with the skin, and the compression significantly influences readings. Color measurements obtained from digitized images have been proposed as a simple and cost-effective way to evaluate skin color and promote efficacy of treatments. The disadvantage is its direct and close relation to the ambient light: even if an accurate control of subject illumination is provided, readings vary between different laboratories. For this purpose, a study proposes a standard system for computerized color image analysis of skin erythrosis modification after Intense Pulsed Light (IPL) treatments, making it possible to compare readings taken by different observers in different environmental light conditions.

Standardized photography is especially important in facial resurfacing procedures where the changes are often subtle and variation in technique may demonstrate a clinical difference where none exists. In dermatologic photography, fine details, such as changes in skin texture, pigmentation, rhytids and pore size, are evaluated to determine the efficacy of facial resurfacing procedures.

## Critical Point and Guidelines

### Photographer

Ideally, a single individual should be designated as the photographer for all pre- and postoperative imaging sessions. This individual must have a basic understanding and ability to operate all equipment in the studio. Larger practices may be able to hire a professional photographer. However, in many cases the surgeon is most attentive to his own imaging needs and will be the best person to photograph patients. A study reports that over 70% of the respondent surgeons were taking digital photographs of patients themselves using their own cameras [10]. Although it may initially seem that photography is a waste of the surgeon's valuable time, additional anatomic observations are often made while taking photos that assist in preoperative analysis and planning. Interactions with the patient during the photographic session may provide valuable and at times interesting insights into the patient's suitability for an operative procedure. Whoever is designated to do the photography must appreciate the importance of consistent camera settings, careful patient positioning and knowing the correct views to obtain for specific procedures.

### Studio and background

If possible, a dedicated space should be reserved for the studio. The walls should be painted a neutral color, preferably soft white. If windows are present, light blocking curtains should be installed. A dedicated photography space improves efficiency, consistency, and patient privacy; however, a consultation room or even a storage area can be utilized if clinic space is scarce.

A medical portrait studio is a useful adjuvant to a facial plastic surgery practice. A studio allows for a permanent arrangement, a consistent approach and a time-efficient method to obtain high-quality photographs.

These considerations are valid, but physicians often must document images in different environments. In this regard, the standardization of pictures can be ensured by an appropriate background.

The purpose of the background is to eliminate distractions and place full focus on the patient. The background must be an even, nonreflecting, monochromatic surface and it should be without folds or creases.

In terms of choice of color, a blue background is ideal for medical photography. A blue background provides sufficient contrast, is complementary to all skin colors, is pleasant to

the eye, allows for a greater depth of field and moderates shadows without overwhelming the subject [11]. Blue works well if the picture is converted to a black and white image [6].

Neutral white and gray are also acceptable choices, but a white background produces harsh shadows, whereas a black or dark gray background provides less contrast, diminishes the image's 3-dimensional quality [12], presents challenges with dark hair and complexions unless a third light source is used to provide subject-background separation.

Once a color has been selected it should not be changed.

## Camera and lens

A multitude of cameras and lenses are available and choosing the correct equipment for own practice can be confusing. In many practices, the surgeon also functions as his or her own photographer. At a minimum, it is important to have a basic knowledge of camera and lens equipment.

The 35mm film has long been the gold standard of medical photography. Indeed, the quality of standard 35mm film images is yet to be surpassed.

However, purchasing, developing, and storing film for a 35mm system has become increasingly expensive, and availability has diminished over the last few years. Recently, Kodak announced that after having manufactured Kodachrome film for 74 years, it would stop soon [13]. Just finding a new 35mm camera to purchase in today's market is difficult, unless one is willing to purchase used equipment.

Given the convenience and broad capabilities of modern digital cameras, more and more physicians are switching to digital systems. Digital cameras offer many new advantages such as instantaneous pictures, ability to crop and adjust on a computer, and provision of images that can be easily stored and filed.

Another clear advantage of digital photography over film is immediate confirmation that the desired image has been captured on the Liquid Crystal Display (LCD) screen.

This quick feedback allows inferior-quality images to be retaken and undesired images to be immediately discarded.

Similar to conventional 35mm film cameras, digital cameras are available in point-and-shoot (compact) and Digital Single-Lens Reflex (DSLR) models.

Although point-and-shoot cameras are less expensive and easy to use, the resolution of these models is generally lower than that of the digital single lens reflex cameras. DSLR cameras also afford the ability to change lenses and adjust settings that control aperture size, shutter speed, and exposure. Certainly, DSLRs are more expensive than point-and-shoot models. The addition of options increases the price, while the learning curve becomes increasingly steeper. Nevertheless, with increased demand and advances in technology, DSLR cameras are becoming smaller, lighter, cheaper, and less complicated to use.

About resolution, while digital technology is approaching the level of resolution of 35mm film (the equivalent of 35 million pixels), a resolution of 1.5million pixels (megapixels) is acceptable for medical photography [12].

Generally, cameras with 5 megapixels or higher are sufficient for the purposes of medical photography [14].

Lens selection is important for taking high-quality photographs and minimizing the amount of distortion. Basic lens types include normal, wide-angle and telephoto lenses. Features such as aperture, zoom, macro and image stabilization vary depending on the choice of lens. Most DSLRs come bundled with a standard wide-angle zoom lens. It is,

however, possible to buy the body and lens separately.

Lenses are classified by focal length. This measurement, defined in millimeters, is the distance between the optical center of the lens and the digital sensor when the lens is focused on infinity. This distance relates to the distance that the camera must be from the subject for the subject to be in focus. So-called normal lenses closely approximate the human eye focal length of 50mm [15]. They are designed to "see" what the human eye sees and are thus ideal for preoperative and postoperative documentation. Wide-angle and telephoto lenses are classified based on the different angles of view they provide when compared with a normal lens.

Most DSLR cameras come equipped with a zoom lens, which allows the photographer to change the focal length without changing lenses.

If working with a zoom lens, it is imperative to use the same focal length for preoperative and postoperative documentation to avoid inconsistencies. Fixed focal length lenses are also available and some authors recommend using a fixed focal length lens to ensure image consistency [16]. Macro lenses are designed for near focusing and allow capture of facial details. For medical portraiture, a macro lens with a focal length of 90 to 105mm is recommended to capture relevant details of facial anatomy [14-16]. The range is extended to 120mm for close-up dermatologic photography [17]. Lenses with shorter focal lengths, such as 50 to 55mm, create a noticeable mid-face distortion.

Last but not least, nowadays the new smartphones offer a useful way to always have in the pocket a light and simple to use camera with high resolution and for this reason are chosen by many physician for everyday medical pictures. In fact in the medical practice is not often possible to program in advance when and where meet the patients (mostly for post-operative controls) and smartphones represents a camera always suitable to use.

## Light

Illumination must guarantee optimal definition of anatomic details and must be reproducible. In a photographic studio, lights are fixed, which is certainly advantageous.

For facial rejuvenation and resurfacing procedures and to capture facial redness and pigmentation, soft, even, diffuse light, devoid of shadows and sharp lines, is used. These lighting conditions are achieved by using multiple flash units and soft boxes or umbrellas, which act as diffusers to eliminate shadows and provide even lighting [11].

In fact, although every camera includes a built-in pop-up flash or can be fitted with an on-camera flash, this method of lighting is unacceptable for medical portraiture. Because facial photographs are taken in the vertical, or portrait, position, camera-mounted flash results in harsh and uneven lighting. Conversely, a ring flash produces flat lighting and should be reserved for intraoperative photography. So, a single mounted camera flash, while inexpensive, will produce harsh shadows and uneven lighting [18]. Therefore, a studio setup of lighting is preferred.

Specifically, the quarter-light system was designed for medical photography, and consists of 2 lights of equal intensity, positioned at 45° from the subject-camera axis [8], with patient placed 50 to 90cm from the background. If unwanted shadows persist despite the use of dual strobes, a third ceiling mounted strobe may be helpful.

Although these simplifications, optimal conditions for obtaining the best definition of surface details without shadow are offered by the following Figure1.

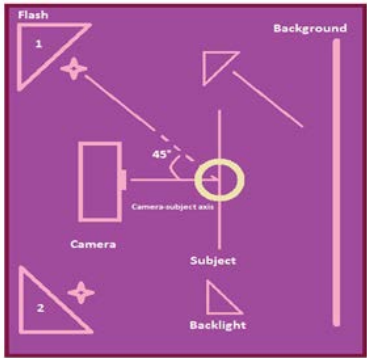


**Figure 1:** Setup for photography for facial plastic surgery. The flashes are set up at 45° to the camera-subject axis. Backlighting provides separation from the background, as does the distance between the subject and background.

• Two lamps at 45° with respect to the patient on a plane parallel to the frontal one.

• One light from above in a sagittal plane perpendicular to the frontal one aiming downward (or two lights at a 45° angle with respect to the subject).

• One light behind the patient on a plane parallel to the frontal one aiming forward and at a distance of 30 to 60cm from the background so as to detach the patient from the background, thus highlighting surface details.

The downside of this system is cost and requirement of a large space.

An understanding of color temperature and white balance is important in achieving appropriate color balance of the images. Different light sources have different color temperatures, containing different amounts of red, green and blue light. White balance tells the camera which combination of red, green, and blue light should be perceived at pure white under given lighting conditions. Because lighting in the medical office studio is often mixed, white balance should be set to automatic to produce truest color results. If all the light in the medical studio comes from strobes, camera white balance may be set to flash [19].

Electronic strobes are ideal light sources for medical photography studio [19]. Other light sources include ambient light, such as overhead fluorescent lighting and tungsten flood lights. These light sources may produce inaccuracies in skin tones.

For example, images taken in fluorescent lighting may have a slight greenish tint to them, whereas tungsten lighting produces a yellow/orange hue. Strobe lights produce light at 5500K, which is sufficient to overpower any uncontrollable ambient light; however, every attempt should still be made to minimize ambient light, both natural and artificial.

Outside a photographic studio, ideal illumination is not easily attained, especially in restricted areas, such as outpatient clinics or operating rooms, where a flash is required most of the time. This supplementary light has a fixed exposure and shutter speed. Once it is switched on and automatically operated, its use does not require other procedures. Care must be taken to position the camera correctly, which is essential to avoid shadows, depending on the position of the flash with respect to the lens. In fact, with the most common digital cameras, it is appropriate to capture the image of an anatomic site with a greater horizontal diameter, maintaining the camera horizontally. Conversely, vertical subjects are photographed with the camera kept in a vertical position such that they are easily included in the vertical rectangular frame of the picture. This rule does not hold true when the flash

is used, except in the case of annular flashes, whose illumination is independent of the camera's orientation and characterized by a low working distance (flash-to-subject) using the macro function horizontal, with the flash on top, in taking frontal views, even of vertical subjects, so as to standardize illumination, with the light always coming from above.

On the contrary, for lateral and oblique views, it is necessary to turn the camera so that the flash is on the side corresponding with the photographed detail.

In this way, for example, when pictures of the face are taken, shadows are not produced by projection of the forehead, nose and lips. Keeping the subject set off from the background helps to avoid shadows as well. An alternative to the flash is adequate environmental illumination, with the same series of shots taken under consistent conditions. Care must be taken because different conditions of illumination, highlighting surface irregularities, can mimic a preoperative-postoperative effect.

## Patients preparation and sequences

After the patient is escorted into the studio, photographic distractions should be addressed. Proper preparation for photo documentation is critical to maintaining consistency and producing photographs that capture the essential anatomic details. The patient's hair should be pulled away from the face to expose the forehead and both ears, and can be accomplished with hair clips or flexible hair bands. Eyeglasses and jewelry should be removed and, depending on the procedure, it may be beneficial to have the patient wear only a surgical gown so collars and distracting clothing do not obscure pertinent anatomic detail [20].

Although some patients may be reluctant, removal of makeup before taking photographs may be required in cases whereby the makeup itself is distracting or excessive. An added benefit is that removal of makeup can reveal skin irregularities or fine rhytids that can be addressed as part of the surgical plan [20].

Facial expression can affect fine details of skin appearance. Smiling can accentuate periorbital wrinkles and nasolabial folds. Neutral facial expression is necessary to accurately access topography of the skin [17]. Importantly, patients should be photographed with the same facial expression, whether smiling or neutral, before and after the procedure.

Imprecise patient positioning is probably the most common error during portrait photography. Articles published in highly regarded journals still frequently contain serial images of a subject from the same "view" when there is obviously great variability in positioning even to the casual observer. Changes in a patient over time following a procedure cannot be accurately assessed unless identical positioning is used during every photography session.

Sommer and Mendelsohn [9] demonstrated that small variation in patient positioning can affect photographic interpretation.

Specifically, neck extension or head protrusion can improve jaw line and reduce the appearance of submental soft tissue. Direction of gaze is also important to obtain accurate photographs. Having patients look up will improve the appearance of periorbital wrinkles [17].

Proper patient positioning begins with the patient sitting erect in the seat. Once the patient's posture is appropriate, the head is flexed or extended to bring it into the Frankfort horizontal plane (an imaginary line from the tragus to the inferior orbital rim that is parallel to the floor). Obtaining the proper Frankfort plane is greatly facilitated by the use of an architectural grid in the camera viewfinder.

Maneuvers to assure that the Frankfort plane is maintained on lateral views include asking the patient to open his or her mouth, while the correct horizontal position is verified by direct line of sight between the oral commissures. An additional alignment safeguard on lateral view is achieved by superimposing the eyelashes and eyebrows [21,22].

There are two descriptions on how to obtain the oblique view. Some advocate lining the nasal tip with the edge of the contralateral cheek. Detractors complain that this alignment results in over rotation of the patient and provides a "five-sixths view in lieu of a three-fourths view." An oblique view with less rotation of the patient can be achieved by aligning the patient's ipsilateral medial canthus to the oral commissure [12].

Magnification of the patient's image should be consistent between photography sessions. This process starts by using the same fixed focal length lens for every session (eg. 105mm). It is also critical to disable lens auto focusing. The photographer should manually adjust the lens to a preselected patient distance and then move the camera toward or away from the patient to achieve sharp focus. The distance setting, or focus adjustment, on the lens barrel should not be altered between shots or sessions as this will result in image magnification inconsistencies.

While maintaining proper positioning and magnification is relatively simple, many find obtaining consistent exposure challenging.

It plays a fundamental role in creating a high-quality image. To obtain consistent exposure, automatic exposure settings should be avoided.

The camera mode should be set to manual and 3 camera variables that determine exposure must be set by the photographer: f-stop setting, shutter speed and ISO. A fourth variable, strobe power is also relevant.

The amount of light that strikes the image sensor depends on aperture setting, also referred to as f-stop and shutter speed. The aperture, much like the pupil of the eye, controls the amount of light that passes through the lens. Shutter speed, much like a blink, determines the length of time the light is allowed to hit the sensor. Proper aperture and shutter speed selection is critical for achieving accurate reproduction of the subject matter.

F-stop number represents the ratio of the focal length of the lens to the diameter of the lens diaphragm opening. The larger the f-stop number, the smaller the diameter of the lens opening, the less light is allowed to strike the camera sensor.

Each f-stop setting lets in half as much light as the next lower setting. The aperture of the camera also affects the depth of field, or the distance over which objects in the picture appear sharply focused. The larger the f-stop, the greater the depth of field. Typically, f/16 is desirable to ensure that all facial features are in focus. Patients with darker pigmentation may require f-stop to be lowered by half to 1 setting to brighten the image [12]. To select an appropriate f-stop for a given studio setup, a series of test shots should be taken at varied f-stops. These images can then be examined to select the appropriate setting. Shutter speed affects the amount of light that enters the camera and controls the amount of movement seen in the photograph. For most photography in the office studio, shutter speed should be set to 1/60 seconds, a standard flash sync speed [16].

ISO setting controls sensitivity of the camera sensor to light. The higher the ISO, the more sensitive the sensor is to light. In medical portraiture, an ISO of 200 is ideal to produce high-quality images.

Standardization of perioperative photography is especially critical for patients undergoing facial resurfacing. Fine details of skin texture, rhytids, pigment irregularities and pore size

need to be assessed with highest accuracy [17]. In addition, maintaining uniformity of patient position, camera settings, and lighting need to be unconditionally consistent. There are 5 standard views that apply to most, if not all, facial aesthetic procedures, comprising the Anteroposterior (AP) view, the oblique view from right and left, and the lateral view from right and left.

These five views of patients are recommended with close-ups of the areas that are to specifically addressed. These procedures often require multiple sessions, and the optimal time point for follow-up photographs is immediately before each treatment [17].

Standard views taken preoperatively apply postoperatively as well. Photographs of patients are usually taken at 1 year after surgery, as by then the patient is completely healed and most of the swelling has subsided. Often, photographs can be taken at shorter intervals for less invasive procedures.

It is critical to maintain a standardization implemented for preoperative pictures to capture the true results of surgery.

Specific Criteria According to Anatomic Area

## Face

**Frontal view:** From the upper limit of the head to the "jugular incisure," with the patient looking at the camera. The line that runs from the right and left tragions (upper edge of the tragus) to the lowest point on the lower edge of the orbit (Frankfurt plane) is horizontal.

**Oblique view (right and left):** From the frontal view, with the patient's whole body rotated 45° so as to align the tip of the nose with the cheek outline. Care must be taken to leave a narrow stripe of cheek to set off the nasal tip from the background. The Frankfurt plane is held horizontal. The patient looks ahead.

**Lateral view (right and left):** From the frontal view, with the patient's whole body rotated 90° so as to align the nasal tip and chin. The head must be in its anatomic position with no lateral inclination, neither flexion nor extension. The Frankfurt plane is held horizontal, and the contralateral eyebrow is not visible. The patient looks ahead. Images must be captured asking the patient not only to assume a neutral face expression, holding a relaxed and natural head position, but also to assess mimic muscular contraction (Figure 2a,2b).

**Figure 2a:** Images in neutral face expression.

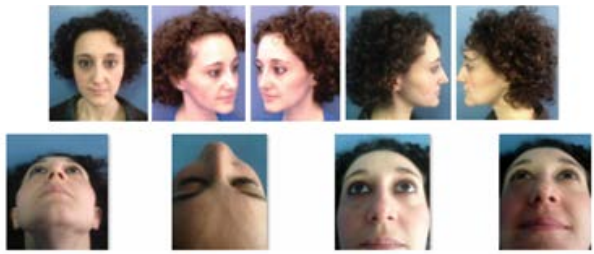

**Figure 2b:** Images in mimic muscular contraction.

**Nose** (Figure 3)

**Frontal view:** The upper limit is the hairline, and the lower limit is the laryngeal prominence. The vertical axis of the face must be perpendicular to the horizontal plane, which is attained by checking eye and ear symmetry as well as by holding the Frankfurt plane horizontal. A lateral slant of the head can convey a false image of the nose, concealing or enhancing its deviation.

**Oblique view (right and left):** The patient rotates 45° with the whole body so as to align the tip of the nose with the cheek outline, leaving a narrow stripe of cheek to set off the nasal tip from the background. The Frankfurt plane is held horizontal and the patient looks ahead. This projection, seen by the patient in the mirror, is essential for assessing supratip deformities.

**Lateral view (right and left):** The patient rotates 90° from the frontal view. The tip of the nose is aligned with the forehead and chin. The ear must be included in the picture. The Frankfurt plane is held horizontal and the contralateral eyebrow is not visible. Both sides are to be photographed.

**Basal view:** The head is bent backward so as to align the nasal tip with medial canthi on a horizontal plane. The frontal eminences and chin are points of reference. This view allows assessment of the nostrils, the nasal base and tip deviation.

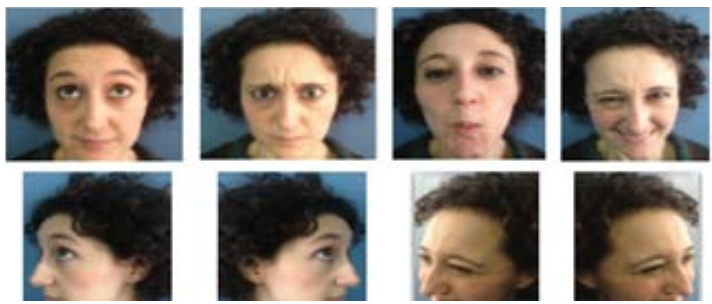

**Figure 3:** Photographic sequence for nose.

**Eyelids** (Figure 4)

**Frontal view:** The same view as for the whole face to show asymmetry, wrinkles and the like.

**Frontal close-up view:** The upper margin is the eyebrows, and the lower margin is the

malar arches. The lateral canthi must be included. Eyelid mobility is to be documented. Pictures are taken of the patient looking up, looking down and with closed eyes.

**Oblique close-up view (right and left):** Patient at 45°. The patient looks ahead, up and down. These views allow thorough assessment of lower eyelid bags. The camera is horizontal.

**Lateral close-up view (right and left):** Patient at 90°. The camera is horizontal. This view showing the position of the eyeball relative to the zygomatic bone is essential to establish whether the vector, according to vector theory, is positive or negative. The vector is the line that runs from the most prominent point of the eyeball to the malar bone. Its position is considered relative to the vertical plane tangent to the malar bone. If at the level of the eyeball the two planes are more than 4mm apart, the vector is positive. If the distance is less than 4mm, the vector is negative. This view allows assessment of the upper eyelid lateral fat pads as well.

**Figure 4:** Some images of photographic sequence for eyelids.

Using the measurement tool of the imaging software, the key landmarks for analysis are first chosen. Soft tissue counterparts for standard cephalometric landmarks and their definitions are as follows (Figure 5).

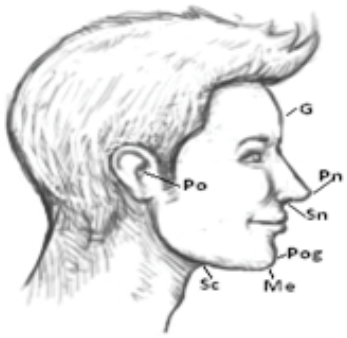


**Figure 5:** Soft tissue counterparts for standard cephalometric landmarks.

- glabella, most prominent anterior point of the forehead.
- infraorbitale, lowest point on the inferior orbital rim.
- menton, lowest point on the chin.
- pogonion, most prominent point on the chin.
- porion, superiormost point of the external auditory canal.

- pronasal, anterior most point of the nose (tip).
- subcervical, innermost point between the submentum and the neck.
- subnasal, point at which the columella meets the upper lip.

When differences in photograph sizes occur and measurements cannot be made in absolute terms, imaging software allows for calibration by indexing for relative measurements between constant landmarks, such as the distance between the porion and the pupil [23]. Another method by which to resize 2 differently sized profile photographs is to calibrate both photographs to the diameter of the iris, which has been shown to be a consistent measurement [24].

After these points are chosen, the measurement tool can then be used to draw lines and obtain quantitative data for standardized facial proportions of interest. A variety of specific angles can be obtained with computer imaging software. The general soft tissue concavity versus convexity of the profile is approximated by the Facial Convexity Angle (FCA). FCA is defined as the intersection of a line from the glabella to the sub nasal, with a line from the sub nasal to the polonium [25]. The angle is affected by adjustments in forehead prominence, horizontal maxillary projection, or chin projection. The Mentocervical Angle (MCA) is created by drawing a line from the pronasale (the nasal tip) to the polonium as it intersects with the sub mental tangent. The MCA is affected by changes in nasal tip or chin projection [26].

The Cervicomental Angle (CMA) is formed by a line tangent to the submentum and the neck tangent intersecting at the sub cervical [26].

## Storage

Digital technology has reached high levels of quality, with its usage becoming dramatically more widespread in the medical surgical field over recent years. Most surgeons have switched to digital photography in consideration of its undeniable assets. It is extremely advantageous for archiving, storing and retrieving images in terms of time and space. Computerized database management facilitates data retrieval.

Its main limits are represented solely by hard disk capacity and usage of peripheral units (eg. CD ROMS). Furthermore, the computerized storage and data transfer eliminate the need for transporting loads of photographs.

Once the camera has captured the image, it is saved to various formats. The most common are Joint Photographic Experts Group (JPEG) and RAW formats. The JPEG format is the easiest to use because the computer in the camera processes the image, discards the extra input and outputs the final image automatically. Benefits of the RAW format include a more detail retention in highlights and shadows and the ability to salvage an image that has been over- or underexposed.

The RAW format, however, is not supported by most image software or printers and therefore, the image must eventually be converted by computer software before outsourcing [27]. In saving the image, there is also the option of a variety of compression ratios. Low compression ratios store more picture information, resulting in higher picture quality. Low compression uses more disk space per picture. Likewise, high compression images result in lower image quality, but because each image takes up less disk space, more photos can be stored on the memory card.

Most digital cameras currently on the market allow the user to set the compression ratio, thereby allowing the photographer greater flexibility in balancing disk space and image quality.

The evolution of photo editing software has emphasized the need for standardized image capturing.

Pictures, if not standardized, must be modified to be comparable with images in similar formats.

However, image manipulation could threaten the very truthfulness and guarantee of image standardization, with all the ensuing consequences (impossibility of comparison and unreliability of results, publications, and presentations), as well as image reliability for medical-legal and insurance purposes.

This is why various software products capable of identifying manipulated images and their artifacts have been introduced on the market.

## Consent

Consent for photo documentation must be obtained prior to any photography. The consent should include a statement describing the justification of the photographs. Patients must understand that their photographs are tools for surgical planning and will become part of their medical record. Additional statements regarding patient confidentiality are necessary if the photographs are to be used for educational purposes, lectures, exhibits and publications [20].

So, consent to photography should be discussed on three levels: firstly, that the image is for the medical record; secondly, that it can be used in teaching; and thirdly, that it can be used for publication and subsequently be accessible within the public domain [28].

Patients can then choose which level of consent they wish to give. Moreover, many journals require written consent prior to publication and issue photography consent forms for patients to sign [29].

In medical photography, the copyright is owned by the "photographer" but a physician cannot capitalize on the use of photos, such as appearance on a physician's Web site, without the patient's explicit permission. Just like any other part of the patient's medical record, medical photographs need to be stored with maximum security measures, requiring password-protected log-ins to prevent unauthorized access [30].

## Conclusion

The central role of photography in the clinical and educational areas of plastic surgery implies adoption of an acceptable level of standardization. The less an image is manipulated, the more reliable it is. Implementation of the simple general and specific criteria proposed allows reasonable standardization of image capturing on behalf of personnel with no particular proficiency in photography.

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# Informed Consent

## Introduction

The informed consent represents the framework of the whole medical practice both from the juridical and from the ethical point of view.

Generally, communication with patients about their medical data is a main ethical task of the physicians. Moreover, the informed consent process is crucial especially in the context of cosmetic treatments [1,2], exerting a strong influence on both patients' perceptions of quality and doctors' risks of experiencing legal disputes.

Some pioneering examples can be found in classic historical documents such as the Hippocratics writings (5-4 BC), Percival's Medical Ethics (1803), the first Code of Ethics (1846-1847) of the American Medical Association (AMA) as well as in studies (books and essays) on medical ethics of XVIII and XIX centuries [3], without univocal opinions about the role of informed consent. Hippocratic reports did not hint at obligation of veracity or disclosure, and throughout the ancient, medieval and early modern period, medical ethics developed predominantly within the profession of medicine. With few exceptions, no serious consideration was given to issues of informed consent and self-determination by patients. The central concern was how to make disclosures without harming patients by revealing their conditions too abruptly and starkly. The emphasis on the principle "first, does no harm" promoted the idea that health-care professional is obligated not to make disclosures because to do so would be to risk a harmful outcome.

Instead, the roots of modern medical informed consent go back to 1914, when a New York judge stated: "Every human being of adult years and sound mind has right to determine what shall be done with his body and a surgeon who performs an operations without his patient's consent commits an assault for which he is liable in damages" [4].

In this way, self-determination came to be the primary justification for legal requirements of attainment of consent from the patients.

The actual term, informed consent, was conceived later in 1957 during another court case, also in the United States [5].

In the late XX century, among the most important publications in the medical literature to appear during this period, there was a statement in 1981 by the Judicial Council of the AMA. For the first time, the AMA recognized informed consent as a basic social policy necessary to enable patients to make their own choices, even if their physicians disagree. The AMA's statement is a testament to the impact of the law of informed consent on medical ethics.

In Italy, the principle of informed consent has been developed from constitution that guarantees the inviolability of individual freedom [6] and the protection of health as a

fundamental right [7]. So no one can be subjected to medical treatment against his will, if such treatment is not expected as mandatory for law.

Also for the code of medical ethics, "the physician should not undertake a diagnostic and/or therapeutic act without the acquisition of the informed consent"; in particular, "he must give to patient the most appropriate informations about diagnosis, prognosis, perspectives and any diagnostic-therapeutic alternatives, and possible consequences of the choices" [8].

After a first orientation of the Supreme Court, that provided informed consent as a pre-contractual phase, this is now regarded as a contractual obligation. In fact, it is part of the complex medical work, in his professional relationship with the patient.

## Informed Consent and Medical Disputes

Plastic surgeons and other doctors who perform cosmetic procedures are more likely to experience litigations or formal complaints than most other specialists [9-11]. Practitioners have attributed this elevated medico-legal risk to a variety of factors, including unrealistic patient expectations, aggressive plaintiffs' lawyers [12], and inadequate preoperative assessment [13] and bad behaviour by a few substandard providers. Patient advocates and other commentators point to the commoditization of medicine [14,15], promotion of suspect aesthetic norms [16], euphemistic portrayal of outcomes [17], and departure from established processes and standards for obtaining informed consent [18].

A recent study [19] reviewed 481 malpractice claims and serious health care complaints resolved in Australia between 2002 and 2008 that alleged failures in the informed consent process for cosmetic and other procedures. This research found that there was a total of 16% of the legal disputes over informed consent involved cosmetic procedures.

This study profiles "real life" situations in which patients undergoing cosmetic procedures perceived the informed consent component of care to have gone so poorly that they were motivated to seek relief through litigation or conciliation.

Why do cosmetic treatments feature so prominently in disputes over informed consent? Most informed consent disputes are about undisclosed risks [2]. It seems plausible that learning the details of risks tends to matter more for patients undergoing treatments towards the elective end of the care spectrum than for those at the urgent end; and intervening on well patients for the purpose of improving or correcting natural variations is the ultimate form of elective treatment. Additionally, complications of cosmetic procedures are usually visible and out-of-pocket payments are common, further reducing patients' tolerance for risk. After undisclosed risk, the next most common allegation was that the doctor had not painted a realistic picture of expected benefits. These legations are likely to reflect a mix of factors: high patient expectations filled by media and other cultural influences; overly optimistic portrayal of likely outcomes by practitioners; and the provision of services to vulnerable or unwell patients who are seeking a "fix" that cosmetic enhancement is unlikely to provide.

Media and manufacturer marketing also help promulgate such views and expectations. Patients would love to have the most minimal treatment that provides them with the most extensive results. Plastic surgeons have a responsibility to establish and accept reasonable expectation standards. We must correct unrealistic expectations; otherwise we may accept liability when we predictably fail to deliver their goal. The balance between acceptable patient selection and unrealistic patient expectations is the central issue of liability with patients. Moreover, some patients desire physical appearance improvements as a symptom of Body Dysmorphic Disorder (BDD) or plastic surgery addiction.

BDD and plastic surgery addiction are psychological disorders that severely affect one's self-perception and those suffering from these disorders often overlap. These disorders, although relatively common, remain under-recognized by health care professionals [20]. The prevalence of these disorders, as well as the severe effects they can cause, requires an in-depth look into the disorders and the effects those disorders have on medical treatment.

Recognized as a psychiatric disorder, BDD involves preoccupation with minor or imagined defects in one's appearance [21].

The majority of people suffering from BDD believe that they have a deformity that requires surgical intervention [22]. Thus, rather than seeking psychiatric treatment to improve their mental disorder, they turn to cosmetic surgery to correct their perceived defects [22]. This course of action, however, is far from the ideal, because a large percentage of BDD patients merely transfer their preoccupation to another portion of their body and become preoccupied with their transferred fixation.

One study indicated that 84% of cosmetic surgeons operated on patients with BDD, having failed to recognize the disorder prior to performing the cosmetic procedure [23].

A similar survey revealed that 70% of plastic surgeons reported having performed procedures on individuals with BDD [24].

These findings are important to take several messages for doctors who deliver cosmetic treatments.

As a result, when screening patients for plastic surgery, it has become increasingly important for surgeons to pay particular attention to the patient's psychological state, especially in light of the doctrine of informed consent and its competency requirement [25].

With regard to patients' competency, the presence of either disorder should render informed consent invalid, as BDD and plastic surgery addiction impede cognitive competency. It is necessary, therefore, for plastic surgeons first to take steps to determine the potential presence of BDD or plastic surgery addiction.

Another message relates to the content of the pre-treatment dialogue. Informed consent is a process, not a signature on a form. Solely providing a laundry list of risks does not adequately discharge the obligation to obtain informed consent [26]. Thus, the tricky question for busy practitioners is which risks should be selected for discussion and emphasis.

In addition, the process through which consent is sought is very important. In one third of cases, patients claimed they felt rushed or pressured, and in a quarter of cases the disputed consent was obtained on the same day as the procedure. The actual content of conversations about risk, however exemplary, may be irrelevant if the dialogue occurs in circumstances in which patients are not given a reasonable opportunity to hear, absorb and consider the information. Allowing some time to pass several days between the initial discussion of risks and the procedure itself is generally desirable [18].

In conclusion, the informed consent process, an integral part of modern health service delivery, takes on special importance in aesthetic medicine [27]. Although cosmetic procedures have lower risks of catastrophic outcomes than many other types of surgery, the informed consent process that surrounds it has "supercharged" elements. High expectations and low tolerance for risk on the patient side meet competitive market pressures on the provider side, and complex social and psychological factors may also be in play.

## Critical Point and Guidelines

In Italy, the Supreme Court gave a kind of guidelines about the information.

In summary, these are the characteristics of a juridically valid informed consent:

A) It must give clear and understandable information to the patient about the recommended treatment, emphasizing the benefits and risks;

B) It must be

**Expressed:** It cannot be inferred for facta concludentia and it is not sufficient if tacit;

**Personal:** It must be expression of therapeutic self-determination, so it is not possible any form of representation;

**Conscious:** It must be given by the patient able to discernment;

**Free:** It must not be the result of coercion, deception or error, and it should not be contrary to public policy and morality;

**Preventive:** It must precede the start of treatment and it is subject to revocation;

**Specific:** It must refer to a specific purpose, only to proposed treatment.

These characteristics are still valid, but the informed consent has different connotations when referring to aesthetic treatments.

This difference has its basis in the well-known principle of the obligation of means and not of results, as for all other medical services.

The Supreme Court admits the difference of the relationship between physician and patient in aesthetics, based on difference of purposes that leads to a difference of information.

In aesthetics, the content of the information must express the possibility of obtaining an effective physical improvement that takes an improvement of social and professional life [28].

The court of Bologna pointed out that informed consent for aesthetic performances should be more comprehensive and detailed [29].

In this context, it may be useful for the physician to take some precautions in order to comply with legal regulations and to prevent disputes.

**Some tricks:**

- Try to get consensus in the presence of witnesses (colleagues, family members of the patient);
- Emphasize the subjectivity of results' perception;
- Emphasize the importance of the follow-up and the fact that the patient has to respects all the requirements and controls, while discontinuity and intervention of other physicians or professionals in the outcome, being able to alter the result, must be considered the conclusion of the physician "duties" and the conclusion of the "contract" between physician and patient.

### How to give information

The use of written information, audiovisual recordings, and other decision aids, as an adjunct to face-to-face discussions, may also strengthen the patient's ability to make an informed decision.

The format and extent are country- and medical system-specific and depend on the jurisdiction under which they fall.

The Code of Conduct provides that consent should be "expressed in writing in cases provided by law and in cases where the particularities of diagnostic and/or therapeutic procedures and the possible consequences about the physical integrity need an unequivocal manifestation of individual will."

However, even when the informed consent, for a specific operation, is not subject to any special condition, writing becomes inevitable to protect the physician. A signed document is, in fact, very valuable where, in the case of a negative outcome, it needs to provide a proof of consent about the medical intervention, the risks and failure's possibility.

Lack of retention and understanding of potential risks of a procedure emphasizes the need to improve communication techniques currently being practiced during the course of informed consent.

Over the last half of a century, there has been a dramatic change in the way that health care providers and patients devise most medical decisions. Paternalism has slowly vanished and in its place has emerged a consent process in which patients are more informed and active participants in their decision making. The broadcasting of a set of facts or the mere action of signing a consent form does not constitute informed consent. Valid informed consent is a process, and, as such, it requires that the health care provider enter into a dialogue that in due course leads to patients appreciating their options, as well as the risks and benefits of the proposed and alternative courses of action.

There are eight learning styles, as defined by Gardner [30]. Three-visual, auditory and kinesthetic are the most useful in educating patients.

Studies have repeatedly shown that most patients fail to recall important elements of the consent process shortly after hearing the information [31-35].

One study [31], in particular, reported a mere 38% recall rate of the preoperative warnings in patients undergoing cosmetic surgery.

Therefore, patients remember less than half of the information provided to them [31,36]. As a result, other modalities of disclosure must be considered if we want to improve this situation, such as providing written or printed material in the form of pamphlets or brochures to reinforce and increase the retention of the preoperative risks discussed.

This, however, is no way a substitute for the face-to-face discussion of all aspects of informed consent with the patient [37].

In light of these findings, for example, a study examined a different method of delivering information pertaining to the potential risks of an elective surgical procedure. More specifically, a simple educational intervention, in the form of an informational pamphlet, is used to ascertain whether patient recall of potential complications is affected.

This may ultimately improve understanding and recall of the potential complications associated with a particular procedure. Printed material is a straightforward and economical instrument that can easily be dispensed to patients in any elective clinical setting. It has been shown that such intervention does improve patient understanding and recall of their treatments and its related complications [38-42]. Other studies have established the presence of lower anxiety levels in patients undergoing surgical procedures and improved overall satisfaction with their management with the use of written material [43,44].

The effectiveness of written information has already been established in the past.

Additional methods, such as websites, videotapes, or other instructional materials, can be evaluated.

The following factors are the legal and moral requisites for the patient to give informed consent:

(1) The patient is legally competent,

(2) Consent is given voluntarily, and

(3) Appropriate and adequate information are given.

The discussion of the potential risks and complications of a treatment plan does not, in itself, constitute informed consent.

### What to say

Surgeons must inform their patients of the following for informed consent to be valid and meet the standard of care:

(1) The nature of the disease, condition, or injury;

(2) The nature, purpose, benefits, disadvantages, and limitations of any treatment plan;

(3) The alternatives of the treatment available, including no treatment;

(4) The risks and complications of the treatment; and

(5) Who will be performing the treatment [45,46].

In case of cosmetic surgery, the patient must be given the opportunity to carefully consider the advantages and detriments of the procedures.

### Who must give information

Physicians and surgeons have a legal and ethical obligation to disclose all of the pertinent information to ensure that the patients comprehend all of these features; this task may not be delegated to non-medical staff. The physician carrying out the procedure does not necessary need to obtain the informed consent himself; however, he or she should ensure the suitability and specialist qualifications of the physician obtaining the informed consent.

### When give information

Attention should also be paid to the process by which consent is obtained, with adequate time for reflection and support for informed decision-making. Further research into patients' perspectives on informed consent should help doctors steer an appropriate course in this challenging environment.

## Conclusion

Therefore, how much is a health care professional to disclose and what is considered adequate? There are two standards that the courts use to judge the adequacy of a physician's disclosure of information to a patient: the reasonable physician standard and the reasonable patient standard. Some states use the former, while others use the latter.

The reasonable physician standard asserts that a physician has a duty to disclose information that any reasonable physician would disclose under similar circumstances. This standard, in principle, is considered contrary to the objectives of informed consent because the primary focus is on the physician rather than on what the patient needs to know.

The reasonable patient standard, on the other hand, asserts that a physician has the duty to disclose information that is material in determining what the reasonable patient would want to know to consent to the proposed treatment. In other words, a reasonable physician will inform his or her patient of all risks a reasonable person in the patient's position would likely consider significant in making his or her decision.

Appendix 1 – Some Specific Format of Informed Consent

In aesthetic medicine and surgery is important to underline, for some techniques, as well as the possible risks, the limits and the temporary nature of the benefits.

Patients, in fact, often underestimate the nature of the medical act in this field and think to solve all their problems in a radical and immediate way.

In the following appendix we propose some informed consent model, specific for treatment.

• Botox

http://www.lilymedspa.com/Forms/consent_botox.pdf

http://olympicplasticsurgery.com/medical-forms/Consent-Forms/Botox.pdf

http://www.thecenterforderm.com/procedures/botox/index/botoxconsent.pdf

http://www.lowcountryplasticsurgery.com/img/patient-forms/consent-botox.pdf

• Fillers

http://www.gollaplasticsurgery.com/pdfs/consent_dermal%20filler.pdf

http://www.stl-psc.com/forms/consent-for-radiesse.pdf

• Laser

http://www.ultrabliss.com/consentForms/masterLaserLightBasedServicesConsentForms.pdf

• Lipofilling

http://www.medretreat.com/templates/UserFiles/Documents/Consent%20Forms/Penang%20Adventist/Consent%20Form-Fat%20Injection-Penang%20Adventist.pdf

• PRP

http://www.searchinpdf.com/reader.php?loc=http://www.prp-sandiego.com/uploads/Platelet_Rich_Plasma_consent.pdf (solo in ambito ortopedico)

• Peeling

http://www.alamohillslaser.com/forms/Chemical_Peel_Consent.pdf

## Appendix 2 – Privacy Policy (47)

Of all the personal data, the management of which is governed by the privacy code, health data are the "disclosing state of health" (and sex life) and then all the positive and negative news and information on the physical conditions and mental health of a person.

Even the photographs "taken in for surgery" were considered personal data by the Guarantor (Newsletter n.240 of 3 to 9 January 2005, which is also apparent that the patient who requires to the nursing home or to the doctor a copy of the medical record must also delivered a copy made of photographic evidence).

The Code allows the public and private organizations as well as health care professionals pay inform data subjects and obtain their consent to the processing of personal data (including medical, as mentioned above) with simplified procedures (art.77, paragraph 1 of the Code).

This disclosure should be preferably written, including via forms ("pocket cards with any attachments folding" says the article 78 paragraph 3), that must contain the information included in Article 13, paragraph 3 of the Code, with any integrations, given orally, related to special treatment. This information may also relate to the processing of data carried out by the substitute physician, or even by a specialist whose performance is required by the general practitioner (or pediatrician) or by the patient (article 78 paragraph 4).

In regard to the processing of personal data, the subject has the right to know about personal data concerning him, even if not yet recorded and communication in an intelligible form of the data and of their origin, the rationale and the purposes of the treatment, to request cancellation, transformation into anonymous form or block of data processed in violation of the law, to obtain, if desired, the updating, rectification and integration of data and to object, in whole or in part, for legitimate reasons, the processing of personal data concerning him.

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## Chapter 4

# Chemical Peels

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## Abstract

"Chemical peel" is a dermo surgical method used to treat skin diseases and blemishes: for this purpose it relies on the use of caustic substances in monosupply or in combination [1-3]. Chemical peels are classified, according to their depth of action, viz. superficial, medium and deep peels. When the substance used during the procedure mentioned above reaches a greater depth, the morphological changes obtained will be more noticeable. However, the depth is also related to a longer healing time and a risk of potential complications. Currently there are a wide variety of caustics available that leverage various types of agents for topical use and at different concentrations. The superficial peels, which penetrate the epidermal layer, can only be used in case of acne, dyspigmentation, photo damage and actinic keratosis. The medium-depth peels which stick to the papillary dermis can be used in the resolution of multiple solar keratosis, superficial scars and pigmentation disorders. The deeper peels, which reach the reticular dermis, can be used in cases of severe photo aging, deep wrinkles or scars. The "peel" procedure may be combined with other dermocosmetic techniques to optimize the results and improve satisfaction in patients, allowing the specialist to tailor the treatment to the individual patient's needs. The success of this method is based on a careful selection of patients as well as on the appropriate use of specific exfoliating agents. If used properly, the "peel" procedure represents an excellent tool to provide valid and comprehensive responses to requests for intervention by the specialist dermatologist or plastic surgeon.

## Introduction

The chemical peel is a dermocosmetic procedure [4] that is carried out through the application of one or more caustics on the skin, which are combined in the same mixture or in sequence, for a time and at a concentration sufficient to induce the appearance of an intense erythema, the destruction of portions of the epidermis and, at times, layers of the dermis in succession.

The procedure is designed to stimulate the physiological processes of tissue repair and this is obtained by a controlled burn [5]: treated tissue regeneration, by these repair mechanisms specifically induced, allows you to treat certain skin diseases and/or blemishes, to obtain an improvement or clinical component healing or resolution, through changes in skin texture, of aesthetic-cosmological defects.

Minimally Invasive Procedures for Facial Rejuvenation
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The effects of chemicals used, depending on the level of penetration achieved in the skin, range from simple detachment of the corneum layer, the destruction of portions of the epidermis or the dermis, to considerable inflammatory reactions in the dermis.

At the level of the epidermis chemical peel, decreasing the cohesion of keratinocytes, results in the removal of the corneum layer of the skin and of the keratinic plug; by increasing cellular turnover resulting in exfoliation, it exerts a moderate lightening effect; it inhibits the activity of the sebaceous glands. In most extreme cases the caustic can coagulate the protein structure of cells (frosting) causing a fundamental renewal of the epidermis, which plays an important role in the treatment of photo aging, hyperpigmentation and scar lesions on the whole.

At the level of the dermis, the peeling treatment causes inflammation with erythema and edema, stimulating the fibroblasts to produce new collagen and glycoproteins, renovating the fibrous component of the dermis.

These effects are modulated by numerous factors that can influence the speed of penetration of caustic, the intensity of the exfoliative reaction, which can be more or less notable, and depth levels attainable.

**Purposes:** The chemical peel is a procedure that, compared with other alternative treatments, offers many advantages. It promotes tissue remodeling and improvement or recovery of certain skin diseases, making them more responsive to therapy at home. This allows you to customize the treatment by enhancing and optimizing the therapy.

Dermocosmetic treatments, on the other hand, develop faithful patients, who more and more often explicitly require this kind of therapy.

The peeling procedure is usually used in the clinical aesthetic setting [6,7] and it finds indications in therapy of several skin disorders [8] such as acne and its eventual scars, seborrheic skin, dyschromies (melasma, chloasma, post-inflammatory dyschromia), rosacea, wrinkles and photo aging (elastosis, actinic keratosis, circumscribed hyperkeratosis, solar lentigo).

The peeling treatment is an effective model of prevention of damage caused by light exposure, with particular reference to dyskeratotic lesion at high oncological potential [9].

## Classification

The chemical peels are classified into superficial, medium and deep according to the thickness of the skin affected and to the concentration of the substance used [10].

This classification is based on the level of deep penetration of substances used, regardless of their chemical structure. The superficial peels involve the skin up to the apex of the dermal papillae, the medium peels affect all the epidermis and the reticular dermis, and the deeper peels concern the medium reticular dermis.

The more frequently used chemical substances, in monosupply or in combination, are: the Alpha-Hydroxy Acids (AHA) [11-15], Beta-Hydroxy Acids (BHA), the Alpha-Keto Acids (AKA), resorcinol, retinoic acid, Trichloroacetic Acid (TCA) and phenol.

The association of a lot of caustics in the same mixture can reduce their concentration, making the peeling treatment more efficacious; reducing undesirable side effects, which are more frequent with higher concentrations of singular products.

The factors that influence the type of substance to be used are clinical indication, the degree of photo aging, the skin photo type, the clinical history and physical examination of the patient.

## Superficial peels

The target of the superficial peels [16-19] is to damage the epidermis without exceeding the first layer of the papillary dermis, which could be interested only by the inflammatory reaction [20]. The superficial peels can be performed on all skin types and phototypes according to Fitzpatrick's classification, but with caution in skin phototypes IV-VI. They are used in the treatment of melasma, acne vulgaris, seborrheic keratosis; they facilitate the clearing of solar freckles [21] and improve skin texture [22]. They can be performed with variable cadence, weekly, fortnightly or monthly.

This category can be subdivided into:

**Very light peels**: They affect corneum and granulosum layers. The most frequently used chemical substances are as follows:

1. Glycolic acid 30-50% [23]
2. Mandelic acid 50%
3. Resorcinol paste 10-30% (applied for a few minutes)
4. Jessner's solution (< 3 successive applications)
5. Tretinoin 1-10%
6. Salicylic acid 10-30% in alcoholic solution [24]
7. Solid carbon dioxide
8. TCA 10-20% (single application)

**Light Peels** [25]: These involve the epidermis down to papillary dermis. The most frequently used chemical substances are as follows:

1. Glycolic acid 50-70% [23]
2. Jessner's solution (4-10 successive applications)
3. Resorcinol paste 40-50% (applied for 30-60 minutes) [26]
4. TCA 20-25%
5. Pyruvic acid 30-40%
6. Salicylic acid 20-30% + TCA 10-15%
7. Pyruvic acid 40% + salicylic acid 30%

The AHAs may be used in a buffered or un-buffered form. It's said that tissue penetration can be greater when the application on the skin is longer and/or in the case of failure or delayed neutralization.

## Medium-depth peels

These results in the destruction of the epidermis and of the total papillary dermis to the top layer of the reticular dermis [27,28]. They find indication in Fitzpatrick skin photo types I-III; in skin photo types IV-VI they may cause persistent hyperpigmentation. They offer good results on the skin texture, on actinic keratoses, wrinkles, scars, melasma, seborrheic keratosis and solar lentigo. The medium-depth peels must be used with caution in the case of both acne vulgaris, for possible exacerbation phenomena, and rosacea for the possibility that there might be a persistent erythema. The interval between one treatment and the next

must not be inferior to one month and may require much longer breaks, depending up on the substance used. The most frequently used chemical substances are as follows [29]:

1. TCA:
   a) 35% (multiple applications)
   b) 50% (single application)
2. Pyruvic acid 50-60%
3. Undiluted phenol 88%
4. Sequential peels:
   a) CO2/nitrogen liquid + 35% TCA (skin phototypes I-IV)
   b) Jessner's solution + 35% TCA [30]
   c) Glycolic acid 70% + 35% TCA [31]
   d) AHA/AKA/Jessner's solution + TCA 10% (3-4) + Tretinoin

The TCA 35% must be applied in multiple layers, until it reaches a homogeneous frost: this can be boosted by using additives, such as methyl salicylate, in order to facilitate penetration. The TCA can be used at 50% in single application with high risks of side effects and complications.

The sequential peel, as for the synergistic effect, allows to reach a greater depth compared to substances used individually, and consequentially resulting in a minor risk of complications.

### Deep peels

They affect the epidermis and the dermis as far as mid-reticular layer. They can be carried out in skin photo types I-II and are indicated in the treatment of deep wrinkles, acneic scars, actinic keratosis, solar lentigo and skin laxity. These peels may cause, for the melanocito-toxic effect of phenol, a persistent post-inflammatory hypopigmentation. The deep peels may be performed at minimum intervals of at least six months. Caustic agents most frequently used are:

1. Baker-Gordon's phenol solution (with or without occlusion) [32-37]
2. Litton's phenol solution (with or without occlusion) [32-37]
3. TCA 50% (plus subsequent applications).

## Biological Effects

The caustic substances used in the peeling treatment produce a series of biological effects on the skin [38]. In the dermis these effects are non-specific because they are noticed in every peeling treatment that acts at that level; instead they can be either specific or non-specific regarding epidermis and appendages specifically in relation to the chemicals used [39].

The biological effects of nonspecific peeling treatments are as follows:

### Epidermis:

- Epidermolysis
- Stimulation of cellular turnover [40]

- Reactive flaking
- Modulation of melanocytic activity and dilution of epidermal melanin
- Thinning of the corneum layer

**Dermis:**

- Inflammation
- Cellular stimulation
- Neosynthesis of the components of the matrix

**Appendages:**

- Comedolysis
- Inhibition of synthesis of sebum

In addition, the caustics stimulate the synthesis of growth factors [41], stress proteins and cytokines [42-44], which cover a fundamental role both in dermal remodeling and in the control of the acneic process.

Specific biological effects of peeling treatments are closely related to chemicals used and are utilized as a guide to the choice of caustic to be used [45]:

**Epidermis:**

Glycolic acid: hyper-hydration of the corneum layer (micro-filler effect)

AHA: inhibition of melanocytic tyrosinase activity (by chelation of Fe, Cu, and Zn)

Salicylic acid: solubilisation of intercellular cement

Phenol, TCA: massive cellular necrosis and subsequent re-epithelialization which start from appendages

Phenol: direct melanocyto-toxic effect [46]

**Dermis:**

Pyruvic acid: fibroblast stimulation capabilities equal to those of the TCA but without ablative effects

**Appendages:**

Pyruvic acid, salicylic acid, mandelic acid, resorcinol: these agents constitute the group of lipophilic substances with high penetration in the pilo-sebaceous follicle and bacteriostatic and anti-inflammatory effects

TCA: sebaceous cell necrosis, miniaturization of the sebaceous gland associated with fibrosis

The biological effects are reflected in a series of clinical effects. At epidermal level you get an increase in brightness and smoothness, with improved skin texture; attenuation of melasma and the clearing of limited pigmented lesions; removal of senile lentigo, dyskeratosis, seborrheic keratosis; greater hydration (mainly due to glycolic acid).

In the dermis, the stimulation can lead to the reduction of scars and wrinkles.

Clinically, at appendages level, you may see as a result of peeling treatment, a reduction in acneic lesions, seborrhea and skin pores.

## Indications and Contraindications

**Indications:** The chemical peel is a dermo surgical method that is able to stimulate cellular turnover, to inhibit the activity of the sebaceous glands and pigmentary system and to selectively destroy portions of the epidermis and/or dermis, even with ablative effects. Pathologies and/or imperfections responsive to this treatment are those associated with altered keratinocyte functionality and anomalies of the pigmentary, dermal and sebaceous system [47].

Clinical case studies, which show the above characteristics falling among the specific indications to peeling treatment, are highlighted in Table 1.

| |
|---|
| • Photo aging [48]<br>-Solar Elastosis<br>-Actinic keratosis<br>-Lentigo<br>-Elastotic wrinkles<br>-Dermatoeliosys |
| • Chronoaging |
| • Wrinkles:<br>-Actinic<br>-Dynamics<br>-From sleep<br>• Dyschromies [49]<br>-Melasma<br>-Chloasma<br>-Post-inflammatory dyschromia |
| • Sebaceous glands hyper secretion |
| • Acne Vulgaris (acute/scars) |
| • Rosacea (Figure 1) |
| • Superficial scars |
| • Post-radiation keratosis |
| • Milia |

**Table 1:** Indications to "Peeling" Treatment.

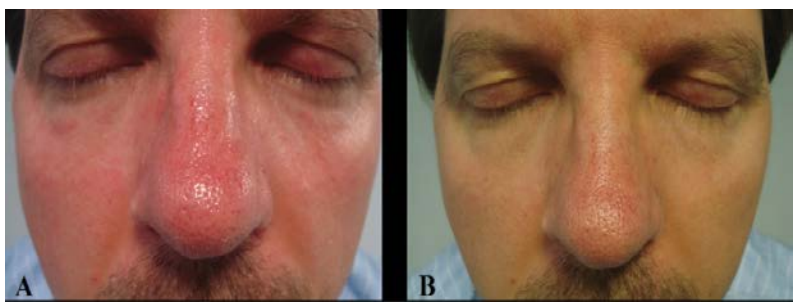


**Figure 1:** ROSACEA (A) before and (B) after two peel treatments with TCA 20%.

**Contraindications:** Contraindications to the peeling treatment are related to the chemical agents used their aggressiveness and programmed depth. It is also important to value the individual characteristics of the patient and the ecosystem within which it operates.

Contraindications found in all types of chemical peels are listed in Table 2.

| |
|---|
| a) Unrealistic expectations and the patient's physical or mental instability |
| b) Herpes simplex in active phase in the skin areas to be treated |
| c) Autoimmune diseases |
| d) Keloids and/or hypertrophic scars |
| e) Previous radiation facial treatments |
| f) HIV infections |

**Table 2:** Contraindications to "Peeling" Treatment.

a) It's always necessary to verify if "peeling" treatment applicants are inspired by realistic expectations and prove adequate psychophysical availability to tolerate both the treatment and the post-peel phase. It is a useful and prudent practice, especially in eager patients, a "spot-test" with the caustic chosen to assess the possible risk of pigmentary outcomes; it should be noted that the "spot-test" is definitely not always predictive and probative. It is essential to check the availability and the capacity of the patient to perform both careful self-treatment and specific treatments of the post-peel phase (such as camouflage, even for long periods, in the case of persistent dyschromia).

b) Extreme caution should be used in recurring forms [50].

c) Systemic autoimmune diseases have an increased risk of slackening of tissue repair, post-peeling hyperchromie, increased susceptibility to infections and vitiligo. Localized forms can induce the "Koebner" phenomenon in the treated area.

d) The feedback of these lesions on the face and on other skin areas is predictive of fibroblastic diathesis.

e) Superficial radiotherapy, damaging the pilo-sebaceous unit, is able to limit or delay the epithelialization starting from appendages, diminishing the regenerative capacity of the skin.

f) Immunosuppression can cause a slackening of tissue repair processes with an increased risk of infection and possible scar developments.

Contraindications to carry out medium and deep peels treatments are listed in Table 3.

| |
|---|
| a) Isotretinoin treatment implemented recently |
| b) Facial surgery recently practiced in the specific area of treatment with tissue separation |
| c) Patients with Fitzpatrick skin photo types IV-VI |
| d) Too thin and inelastic skin |
| e) Heart or hepato-renal diseases [51] |
| f) Smoking |

**Table 3:** Contraindications to Medium/Deep "Peeling" Treatment.

a) It is recommended that the range from interruption of oral therapy with retinoid should not be inferior to 12 months.

b) It is necessary to wait for about 6-12 months as a wide gap may impair cutaneous vascularization which interferes negatively in the healing process.

c) Some patients may present a persistent reactive hyperpigmentation.

d) A thin skin texture with obvious loss of elasticity can react to a peeling treatment by developing a scar retraction.

e) Notably, phenol peels in patients suffering from heat or hepato renal diseases can cause cardiac arrest [52-54] or serious irreversible damage to such organs.

f) Changes caused by excessive smoking (reduced blood circulation and peripheral stimulation of metallo proteinases, that break down the connective tissue scaffold) may interfere with the process of re-epithelialization, favouring the appearance of scars or determining the therapeutic range contraction with anticipated return of wrinkles.

## Stages of the Procedure [55-57]

### Patient preparation

Before embarking on a peeling treatment, practitioner must clearly demonstrate the results that can be obtained with the chosen procedure, avoiding unrealistic expectations. The operator must describe the various stages of treatment analytically from home preparation to patient care, detailed rules for the application of caustic, the post-peel phase, possible side effects and healing times.

A correct approach to the procedure involves the following steps [58]:

Patient Information and Compatibility between expectations and results.

Signing the informed consent.

Photographic documentation before, during and after treatment.

Topical and/or systemic Cosmetic-Pharmacological treatments prescription.

### Skin preparation for the chemical peel

Skin preparation for the chemical peel involves two phases: pretreatment and pre-peeling.

**Pretreatment:** In the 2-4 weeks before the peeling procedure, the patient must respect a series of requirements that, along with those of the post-peel phase, permits to obtain a reliable procedure management.

The pre-treatment consists of topical treatments that have the followings functions [59]:

- Reduce the thickness of the corneum layer in order to promote the uniform penetration of caustic.
- Induce the dermo-epidermal cell turnover in order to prepare cellular compartments to stimulate the peeling procedure.
- Induce blocking of melanocytic activity.

Caustic agents that are more frequently used in this phase include topical retinoids, retinol, AHA [60], BHA, AKA, hydroquinone and other lightening substances such as azelaic acid [61], kojic acid, phytic acid, vitamin C and arbutin.
The type and duration of treatment are related to skin photo type and to the pathology to be treated.

A careful photo protection of all skin photo types is recommended because the pre-treatment causes thinning of the corneum layer, making the skin more sensitive to UV radiation.

In case of previous herpetic pathology riacutization, it is useful to provide 1g of valacyclovir 1 hour before the peeling treatment and then once a day for seven days.

Performing a medium-depth peel, premedication is recommended with lorazepam (1-2 mg per os) the night before and the day of the treatment; in these patients, it is possible

to associate lidocaine 2.5% and prilocaine 2.5% cream for at least 30 minutes during the pre-peeling phase.

A week before the peeling treatment, it is necessary to avoid any type of hair removal, the use of masks and exfoliating facial treatments, hair dyes and the so-called "perm". A skin deep degreasing at home should be avoided so as not to excessively reduce the thickness of the epidermal barrier, with an emphasis on young patients that have a greater inclination to atopic diathesis than others.

Clinically, to prevent hemorrhagic phenomena in the area of the application of caustic, the anticoagulant therapies should be suspended, whenever it is possible. If peeling treatments require analgesia, using anesthetics added with adrenaline, the practitioner should investigate if the patient is in treatment with medications such as propranolol, phenothiazine, tricyclic antidepressants, monoamine oxidase inhibitors, because such products can lead to hypertension and heart problems.

**Pre-peeling time:** It is a set of procedures performed by the practitioner immediately before treatment, which are designed to facilitate a uniform and deep penetration of caustic substances. This phase includes:

- Patient's skin cleansing and possible application of topical anesthetics to soothe burning sensation or pain.
- Removal of every benign keratosic lesion before starting peeling.
- Careful selection of caustics to be used.
- Technical modalities of application:

-selection and appropriate use of different applicators for the procedure: cotton sticks, pressed hydrophilic cotton buffers, brushes palette, gauze, gauze tablets;

-time and frequency of application

Currently it is difficult to encode an elective choice of the caustic agent to be used in relation to pathology or imperfection to be treated, because there isn't a recognized standardization of available and efficacious treatments. For such reasons, the operator's experience represents the cornerstone for an appropriate choice of the substances and relative results obtained.

Rules for the application depend on the type of caustic and the depth that you want to achieve and affect both the capacity of penetration and the consistency with which exfoliate substances spread at tissue level [62].

In order to prevent an excessive penetration of some agents, it may be necessary to apply a timely neutralization of them by diluting such substances with water or with 10% bicarbonate in water.

In case of an accidental fall of caustic into the eye region, immediate eyewash should be carried out by using saline or mineral oil in case phenol has been used.

## The post-peel period

Post-peel period management is strictly dependent on the depth reached by treatment and by the patient's subjective needs [63].

In superficial "peeling" treatments it is sufficient to follow common rules of photo protection accompanied by an adequate tissue hydration.

In deep "peeling" treatments, medication with antibiotics, antivirals, topical glucocorticoids, fatty and gauze bandages may be necessary because they can facilitate re-epithelialization, and then the "restitution and integrum" of the skin. When healing occurs, it's

strongly recommended the use of shielding materials, the application of which must be repeated at least every two hours; in some cases the photo protection can be associated with depigmenting treatments, retinoids [64], AHA, and in selected cases topical steroids.

It is a good idea, for a controlled and safe management of the side effects caused by "peeling" treatment, and to keep strictly to rules of broad consensus, which is critical to patient safety and safeguard the professionalism of the operator.

Even though respecting these rules, they may cause unwanted effects, represented by both side effects and complications [65,66]; their appearance is directly proportional to the depth of "peeling" treatment.

Side effects of chemical peels, which are almost always present, are the clinical manifestation of several stages of the normal healing process after the burn caused by application of caustic on the skin. These are skin reactions whose intensity is variable, correlated to the type of substances used and the individual response. They are temporary and disappear as soon as the phase of tissue repair is completed. The most popular side effects are the following: local erythema of different intensity associated with burning or heat sensation; disepithelization and transient flaking with variable chromatism until brownish color, followed by re-epithelialization; pain, edema, vesicular and crusted lesions, usually presented in the medium/deep peels.

Complications are instead represented by aesthetic lesions which persist for a long time or, in some cases, are permanent [67]. They can be considered either an expression of an altered scarring during "post-peel" phase or due to the presence of no foreseen or no prevent allergies, infectious [68] or toxic factors. However, complications represent an uncommon event, that can occur more frequently in superficial "peeling" than in medium or deep ones (peels). A classification of complications [67,69] is summarized in Table 4.

| |
|---|
| 1.Infections:<br>a) reactivation of Herpes simplex<br>b) fungal infections<br>c) bacterial infections by ascribe to colonization of *Streptococcus* or *Staphylococcus* on squamous-crusted formations induced by the procedure |
| 2. Discoloration:<br>a) hyperpigmentations<br>b) hypo pigmentations |
| 3. Persistent erythema |
| 4. Increased sensitivity to cold after cryo-peel |
| 5. Delayed healing |
| 6. Scar tissue |
| 7. Ectropion [70] |
| 8. Acne |
| 9. Itching |
| 10. Allergic reactions |
| 11. Depression |
| 12. Systemic toxic effects [71-73] |

**Table 4:** Classification of Complications.

## Caustic Materials

Among the substances most commonly used for a "peeling" procedure are:

- Salicylic acid
- Mandelic acid

- Trichloroacetic acid
- Pyruvic acid

### Salicylic acid

Salicylic acid is an aromatic organic carboxylic acid found in willow bark, which has antiseptic, comedolitic and anti-inflammatory properties.

Thanks to its strong lipophilicity, salicylic acid penetrates in the lumen of sebaceous gland in which it exerts a comedolysis higher than that of the AHA, as well as a sebostatic and antimicrobial effect.

In the epidermis, salicylic acid reduces the keratinocytes' cohesion until epidermolysis; it normalizes the keratinocytes' differentiation; it mobilizes the melanin; it antagonizes the expression of the p53 protein and neutralizes free radicals.

In the dermis it has an anti-inflammatory action and stimulates the synthesis of the intercellular matrix components.

Peeling with salicylic acid is used on the face in the form of alcoholic solutions [74] from 10% to 30%, and also as pastes, at various concentrations and on different areas of the face. It is well-tolerated by persons belonging to every ethnic group and to every phenotype, although it should be used with caution in higher skin photo types to avoid discoloration.

The main indications are comedonal or papulopustular acne [75], moderate "photo aging" [76], seborrhea, rosacea, freckles and superficial melasma.

Peeling with salicylic acid is absolutely contraindicated in patients with allergy to salicylates, during pregnancy and in patients that are following an oral retinoid therapy. Other contraindications include infections, inflammatory dermatitis, connective tissue disorders and xerosis.

In "photo aging", acne and Fitzpatrick skin photo types I-III, pretreatment is recommended with topical retinoids for 2-6 weeks until few days before treatment in order to thin the corneum layer, to reduce melanin and to promote the reparative processes [77,78]. In skin photo types IV-V, melasma and PIH, retinoids must be interrupted at least 1-2 weeks before the treatment to avoid excessive inflammatory reactions. In individuals with sensitive skin it is preferable to use cosmetics containing alpha hydroxyl-acids; to treat discolorations and to prevent PIH it is advisable to use depigmentanting substances (4-5% hydroquinone, arbutin, licorice, kojic and azelaic acid) for 2-4 weeks before the treatment.

The acid application is carried out with a fan-shaped brush or with a pad of cotton and/or sponge, repeating the passage on the skin for 2-3 consecutive times and leaving the solution acting for 3-5 minutes. During the procedure, the patient feels a burning sensation which ends after 1-3 minutes; after about 30-60 seconds, at morphological level, you'll appreciate the appearance of a uniform "pseudo-frost" due to crystallization of the acid. The removal may be performed with water or with a solution of baking soda dissolved in water.

In the post-peeling period you must use moisturizing and soothing products as well as a photo protective solution. In the case of unwanted "frost" you might use non-fluorinated topical steroids.

Xerosis, burning and transient flaking with variable chromatism until brownish in color should be mentioned among the possible side effects. Possible complications include crusting and discolored outcomes in cases of prominent "frost", and salicylism when pastes are used at 50% or 20% solutions deployed on at least half of the body surface.

## Mandelic acid

Mandelic acid is an 8-carbon alpha-hydroxy acid, derived from hydrolysis of bitter almonds extract. Mandelic acid taken orally has long been used as a urinary disinfectant. Its antiseptic properties, combined with its biochemical characteristics, which are similar to those of glycolic acid, enhance its complementary therapeutic role, being used as monotherapy or in combination with other acids, in the peeling treatment of minor acne, mild "photo aging" and hyperchromia.

In the epidermis this acid reduces the cohesion of the corneocytes with a modest epidermolysis; it mobilizes the epidermal melanin; it accelerates the cellular "turnover" causing reactive flaking and thinning of the corneum layer.

At the level of the pilo-sebaceous follicle the mandelic acid penetrates into the lumen of the sebaceous gland in which performs a comedolytic, sebostatic and direct bacteriostatic activity. In conclusion the main pathogenic mechanisms of acne are inhibited.

In the dermis it exerts a specific anti-inflammatory activity.

The peculiar properties of this peeling agent (antimicrobial, anti-inflammatory, sebostatic and mildly keratolytic effect), the improvement which it induces on the texture and on the brightness of the skin, and the reduced side effects (no systemic effects, mild local erythema sometimes associated with burning sensation) make it a particularly valuable tool in the therapeutic baggage of the dermatologist in order to treat disorders such as acne, seborrheic skin in generally, rosacea and mild photo aging [79,80].

Peeling with mandelic acid is always well tolerated and has few contraindications, including herpetic infections, the presence of ongoing microbial and/or fungal skin infections, the susceptibility to form hypertrophic scars, the psychotic "habitus" of the patient. Care must be taken in the use of caustic even in patients with dark skin photo types.

The mode in which it carries out the treatment with peeling mandelic acid is as follows: the skin of the patient's face is cleaned either with a solution of ether and alcohol if there is an intensely seborrheic skin, or with a non-aggressive detergent solution if the skin is particularly sensitive. The application of the acid is done with a brush, in succession and quickly on all areas to be treated. After a time ranging from 5 to 15 minutes we can observe the emergence of a slight erythema accompanied by a modest subjective feeling of itching and slight burning. Then mandelic acid is removed thoroughly cleansing your face with running water, keeping the eyes tightly closed; and followed with the application of a fluid soothing lotion.

In the post-peeling period it is recommended to use a moisturizing cream, to sooth lotions and sunscreen. After about 5-7 days the patient may resume using the products adequate to the treatment of the underlying disease.

The peeling procedure with mandelic acid does not have systemic effects and/or complications. Within 3-7 days after the treatment a thin flaking furfuracea can occur, sometimes associated with a mild erythema, which disappears within 1-2 days.

## Trichloroacetic Acid (TCA)

Trichloroacetic acid is a synthetic acid, with two carbon atoms, which occurs in crystalline and highly hygroscopic form. The action of the TCA is expressed through the coagulation of skin proteins. It has extreme keratolytic, sebostatic, lightening and dermoplastic activities due to fibroblast activation and subsequent stimulation of the synthesis of glycosaminoglycan, new collagen and elastic fibers [81,82].

In the epidermis the TCA causes a coagulation of proteins characterized by a white ice ("frost") color of the affected skin followed by dehydration, a corneocitaria necrosis with interstitial responsive edema, an exfoliation followed by hyperkeratosis and a re-epithelialization starting from skin appendages.

At the level of skin appendages, the TCA in particular causes the necrosis of the sebociti, the subsequent miniaturization of the appendage with fibrosis, and a resulting sebostatic effect.

In the dermis the TCA stimulates fibroblast activity, the synthesis of collagen, hyaluronic acid and the rearrangement of elastic fibers.

The action of the TCA depends on its concentration and on the composition of the solvent in which it is dissolved [83-85]: the ideal solvent is water, while ethyl alcohol and the gel formulation make its penetration slower; distribution of TCA becomes more homogeneous by using the gel preparation. In order to get good results, the pretreatment is of paramount importance, including the number of steps taken and the type of skin to be treated.
The TCAs are employed in both superficial peeling treatments, using oscillating concentrations from 10 to 35% and medium-deep treatments, with concentrations ranging from 35 to 50% [86,87].

Among the possible indication of superficial peels are mild and moderate "photo aging" [88,89] (1-2 according to Glogau classification), seborrheic keratosis, thin keratosis, discolorations (epidermal melasma, PIH, freckles, ephelides), acne, seborrheic skin and eritrosys [90].

Medium peels indications include advanced "photo aging" [88,89] and moderate scarring acne (Figure 2-4).

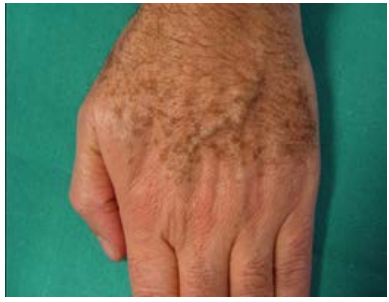

**Figure 2:** Hyperpigmentation of back of the hands.

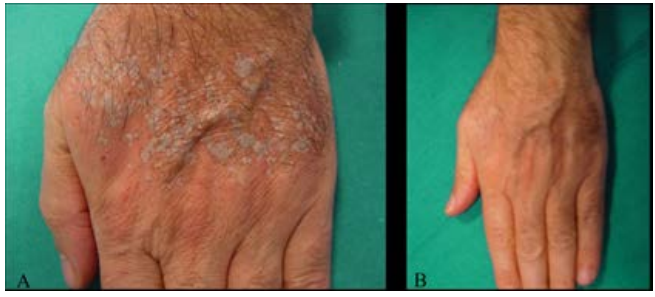


**Figure 3:** (A) Peel with TCA 30% (B) Result after 1 treatment.

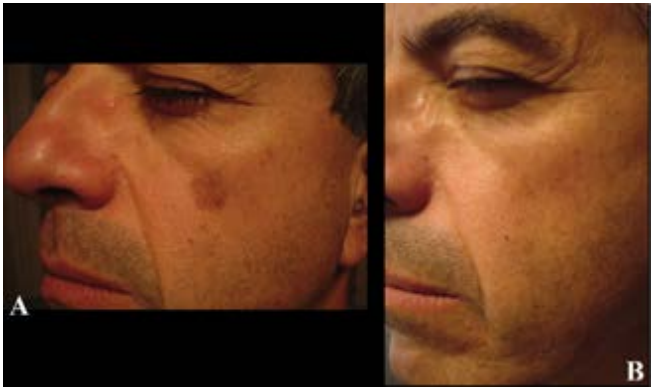


**Figure 4:** (A) Hyperpigmentation of the cheek (B) Result after 2 peel treatments with TCA 20%.

As the re-epithelialization post-peel phase starts from skin appendages, in treating different areas of the face, where their concentration is much lower, practitioner should use low concentrations of TCA in order to avoid the risk of scarring lesions.

The following patients must be excluded from treatment with TCA: patients who have been treated with isotretinoin in the last 8-12 months, patients irradiated and with sub sequential destruction of adnexal structures, patients suffering from herpetic lesions, patients with risk of keloid scars formation, patients who have had "lifting" of the eyebrow in the three months before or patients who have had repairs by cutaneous or muscular flaps capable of altering the normal tissue vascularization.

Other contraindications: pregnancy, diseases of the connective tissue, ongoing cutaneous microbial and/or fungal infections, unrealistic expectations on the part of the patient and the dark skin photo types.

An essential procedural rule predicts that the peeling depth must be proportional to the severity of photo aging according to Glogau classification and inversely proportional to the photo type according to Fitzpatrick classification, as photo types 4, 5 and 6 have a high chance of developing hyperpigmentation in the post-peeling phase.

The pretreatment of the skin is important in order to prepare the different cellular compartments for caustic stimulation, in order to favor a homogeneous substance penetrating through the thinning of the corneum layer and to prevent the post-inflammatory hyperpigmentation phenomena. The substances used for the pretreatment are: topical retinoids, alpha and beta hydroxy-acids, ketoacids, hydroquinone and other lightening substances such as azelaic acid, kojic acid, phytic acid, vitamin C and arbutin. Topical retinoids are responsible for the stimulation of fibroblasts with subsequent production of collagen and hyaluronic acid; they also stimulate the proliferation and differentiation of keratinocytes by deleting those genetically altered and thinning of the corneum layer. Fruit acids and beta-hydroxyacids reduce seborrhea, make the corneum layer thin, reduce corneocitaria cohesion and increase the elimination of transdermal melanin. Depigmentanting substances are important in the process of melanocyte-suppression, which is vital in the treatment of photo types 3-6 to reduce the risk of PIH. The melanocyte-suppression should always be combined with an adequate photo protection.

In thin and sensitive skins the preparation must be particularly gentle to limit the risks of excessive and unwanted penetration.

The procedure starts with degreasing the skin with alcohol or acetone whose application must be prolonged for a few minutes in order to obtain adequate cleaning and degreasing of the skin. In medium peeling you must apply an anesthetic cream [91] for at least 15 minutes, which is then removed with water by drying the affected skin area. Medium/deep peelings may require sedation with diazepam at a dose of 5-10mg (per oz.) orally.

The peeling solution is then applied with the aid of gauze or hydrophilic cotton swabs, not overly soaked in order to avoid the solution's drip. Anatomical areas of the face, which are usually treated, are divided into cosmetic units: the application sequence regards forehead, temples, cheeks, chin, upper lip, nose and eyelids. The depth of treatment will vary depending on the concentration of the acid, on the application mode (single or repeated passage) and on the pressure exerted by the applicator.

After the application of the acid, bleaching of the treated skin occurs. This morphological case comes up with different chromatic intensity levels [92]:

a) "Frost" irregular white rosy: very superficial peeling. The skin is erythematous with a white haze spread, streaks or stains.

b) "Frost" uniform white: superficial peeling. Bright white ice that gives an insight into the underlying erythema.

c) "Frost" compact white: medium peeling. White opaque highly dense and compact, which is the expression of the interest of the reticular dermis; that level is the desired goal in treating severely damaged and thickened skin [93].

d) "Frost" greyish opaque white: peeling comes at a considerable depth, with risk of scarring.

After applying the TCA on an anatomical area, you must wait for the appearance of the "frost" and the planned color: if this does not occur within 2-3 minutes, repeat the application. The number of steps taken is important for the depth to be achieved; during the treatment of the subsequent anatomical units pay attention to not overlap the acid on the border areas.

At the end of the procedure it is recommended to repeatedly apply gauze soaked in cold water over the treated areas to provide relief and dilute the TCA, followed by direct application on the skin of a fluid product with moisturizing and emollient properties. After a few hours it is possible to cleanse your face with a gentle product while the use of a moisturizing fluid should be continued for at least 4-5 days; subsequently it can be replaced by an oilier moisturizer cream.

The re-epithelialization phase begins around the 2-3 day and it is characterized clinically by a parchment and brownish appearance of the epidermis, resulting in excoriation that can extend up to 7-10 days, depending on the depth of the peeling treatment.

The patient must not forcibly remove the exfoliated skin in order to avoid the appearance of persistent erythema, discoloration, altered scarring. A prolonged erythema, that is an indication of hypersensitivity, may find it beneficial to use topical steroids of low strength.

The patient should be photo protected for the entire interval between two successive treatments over a period of at least 6-8 weeks after the last application.

Superficial peeling treatments with TCA may be repeated at variable intervals of 2-4 weeks; medium treatments at intervals of 4-8 weeks and deep ones in at least 3-6 months.

This time is calculated according to the end of the remodeling process, the concentration of TCA and its possible associations.

There is no systemic side effect. Locally an intense erythema associated with burning sensation can be observed and a strong, transitional and brownish color flaking.

The possible onset of complications is closely related to the concentration of the acid and its ability to induce an intense inflammation and ablative effects. It is mainly TCA at concentrations exceeding 30% to show an inflammatory and ablative capability: therefore these formulations have a high risk of post-inflammatory persistent hyperpigmentation, or previous herpes infection reactivation. Rarely cicatricle reactions may occur.

It should be noted that uneven penetration of TCA can cause alteration of the skin "texture", characterized by increased porosity, orange-peel skin and the eventual appearance of milia. Telangiectasia, if present, can be highlighted or even worsened after deleting dyskeratotic injuries.

Anxious-depressive state can represent a serious complication in those patients who are unable to manage the side effects or possible complications of a particularly aggressive peeling treatment.

### Pyruvic acid

Pyruvic acid is an alpha-ketoacid with three carbon atoms containing a ketone group in alpha position which makes the molecule unstable.

It is a very potent substance that can be used as a peeling agent [94,95]; it is highly lipophilic and has antibacterial and keratolytic activity.

Pyruvic acid is present in nature in fermented fruit, apples, vinegar and it enters in the Krebs cycle. In the presence of water, pyruvic acid is always in dynamic equilibrium with lactic acid, its corresponding alpha-hydroxy acid, used for many years as an anti-microbial and sebostatic agent: pyruvic acid therefore has both the characteristics of an alpha-hydroxy acid and those of an alpha-ketoacid.

Among its properties must be mentioned, powerful keratolytic action resulting in thinning of the corneum layer (as opposed to the TCA that produces a reactive hyperkeratosis); sebostatic action without miniaturization of appendages which is observed after the use of TCA; antiseptic and lightening effects. It has dermoplastic action: it activates fibroblasts and stimulates neo synthesis of glycosaminoglycans, collagen and elastic fibers; it decomposes to acetaldehyde and carbon dioxide whose vapors can be irritating to the mucous membranes but non-toxic; finally it can promote, if pure, epidermolysis in about 30-60 seconds and dermal necrosis in about 120-200 seconds.

The action of pyruvic acid depends on several factors: composition, ratio of the relative quantities of alcohol and water in the solvent, skin type, degree of pre-treatment skin hydration, modalities and times of application.

Commonly used pyruvic acid formulations are 40, 50 or 60% in alcohol solution; the concentration of 70% shows a powerful restructuring action on the dermis but must be handled with extreme caution and with expertise to prevent the occurrence of scar tissue.

At relatively low concentrations (40-60%) it operates at three levels. At the level of the epidermis it causes mild hydration of the corneum layer, a decrease of the cohesion between keratinocytes, loss of corneocyte cohesion up to acantholysis resulting in thinning of the

corneum layer. It has a lightening effect because of the mobilization of epidermal melanin. It also accelerates cell turnover with reactive flaking.

At the level of the pilo-sebaceous follicle pyruvic has a bacteriostatic effect on *P. acnes* and comedolitic action. It is a powerful sebostatic and therefore reduces the oiliness in people with seborrheic and/or acneic skins.

At the level of the dermis, it stimulates fibroblasts activity with intensity equal to that of the TCA. It shows anti-inflammatory and trophic effects on vessel walls.

It is very probable that part of the characteristic actions of this exfoliant substance is mediated by stimulation to the release of cytokines [96].

Multiple applications of the product, at low concentration, can lead to a whitening of the skin ("frost"), a sign of the acid penetration down to papillary dermis. Often in dermatological practice, in order to obtain satisfactory results, it is sufficient to provoke an intense erythema.

At concentrations exceeding 60%, pyruvic acid is able to penetrate more deeply with more intense effects, although less specific, up to cause a strong epidermolysis with clear dermo-epidermal separation. At concentrations equal to or greater than 70% pyruvic acid can cause necrosis and cicatricle injury.

The most important indications of "peeling" treatment with pyruvic acid include: active acne [97], acneic scars [98], rosacea, seborrheic skin, actinic keratoses, post-inflammatory hyperpigmentation, superficial wrinkles and "photo aging". It doesn't require any kind of sedation or anesthesia.

It is proven that the peeling treatment with pyruvic acid to 40, 50 or 60% is reliable with a low risk of side effects, well tolerated by patients, who can continue to lead a normal life in the post-peel period. The 70% preparations are useful in treating cicatricle injury and "photo aging" but their use, by inexperienced hands, can cause permanent cicatricle injury (Figure 5).

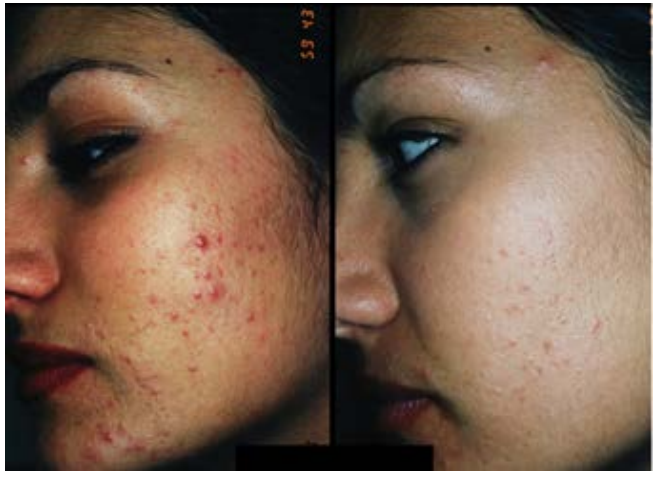

**Figure 5:** Peeling with 40% pyruvic acid.

Due to its strength, pyruvic acid can be compared only with TCA: these two acids have the same ability to stimulate the dermis, but treatment with pyruvic acid is less painful and causes fewer side effects. On the other hand, TCA as compared to pyruvic acid causes the

miniaturization of appendages and has a greater ablative effect on the epidermis, allowing longer lasting effects in acne treatment and "photo aging". Finally, it should be noted that while the TCA peel is self-extinguishes, pyruvic acid peel must be neutralized after a period, the duration of which depends on the strength of the concentration used and on the experience of the operator [99].

Contraindications are those common to other peeling substances.

During the cleansing of the skin and before applying caustic it is necessary to take into account the following factors: high lipophilicity of caustic and high power. So a young person should cleanse the skin with water and mild detergent, without applying creams or make-up. The skin of an older patient, on the contrary, must be cleaned with alcohol to facilitate the penetration of caustic.

After the even application, practitioners have to wait for the appearance of an intense erythema or for the beginning of "frost" and to ventilate the patient's skin in order to ward off acidic vapors. Then proceed with tamponade of the skin with baking soda at 10% in aqueous solution and finally apply, in case of aggressive peelings, apply gauzes soaked in cold water for a few minutes. Once the gauzes have been removed, soothing cosmetics with a high anti-inflammatory action can be applied.

During the post-peel period, it is recommended to use a hydrating-soothing fluid for 7-10 days and the photo protection is always strictly recommended.

The agent is generally well-tolerated and does not cause systemic side effects. Locally we could observe the appearance of an intense erythema associated with a rapid burning sensation; following an intense flaking, sometimes of brownish staining in more intense exfoliation treatments.

Complications have been rarely observed except for the peeling with pyruvic acid at concentrations exceeding 70%. The complications of this type of peeling are represented by: post-inflammatory hyper-pigmentations especially in darker skin photo types; possible reactivation of herpes infections; epidermolysis up to circumscribed necrosis, with discolored and scarring outcomes.

## Combined and Sequential Peels

### Combined peels

Combined peels are characterized by the presence of two or more caustics in the same formulation (alcohol solution or paste). The aim is to obtain, through the use of low concentrations of various substances, clinical and aesthetic results which are comparable to those achievable with the use of each caustic alone at higher concentration, reducing side effects and avoiding possible complications [100] (Figure 6).

Chemicals that are frequently used in combined peels are:

1. Jessner's solution (salicylic acid + resorcinol + lactic acid) [101,102]
2. Pyruvic acid + Mandelic acid
3. Pyruvic acid + TCA

The simultaneous presence of two or more substances attenuates the caustic aggressiveness and speed of penetration of a caustic substance by using a second caustic as an an-

tagonist. It also brings in more depth a caustic substance by using a second as a “carrier”, and to strengthen metabolic and bacteriostatic effects of various substances.

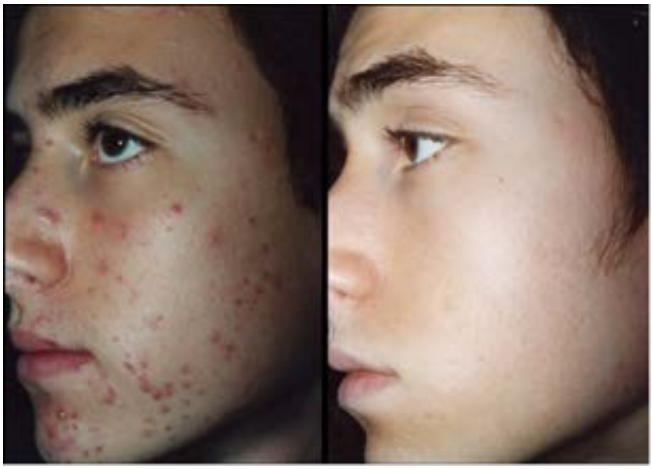

**Figure 6:** Combined peel: Pyruvic acid + Mandelic acid (after three subsequent treatments).

The combinations have a greater manageability, even on sensitive skin; practitioner can lengthen the time spent on the tissue with much reduced possibility on side effects.

Acne, seborrheic skin, scars, and skin wrinkles are the indications for combined peels method [103].

Contraindications include fungal or bacterial infections, viral infection, connective tissue disease, predisposition to hypertrophic scars, chemotherapy and/or radiotherapy, psycholability, dark skin photo types (IV-VI according to Fitzpatrick classification), allergies to salicylates or resorcinol in case of combinations containing resorcinol.

Excellent results can be obtained by combining the pyruvic acid + mandelic acid peeling treatment with photodynamic technique performed by 5-ALA 10% in cream after one week.

## Sequential Peels

Sequential peel aims to realize both superficial peels characterized by reduced inflammatory reaction or almost absent (cold peeling*)* and medium/deep peel [104]; in this case we can observe the same results obtained by using TCA 50% but the risks of the procedure can be minimized. The TCA at high concentrations, if used by inexperienced personnel, can cause scars and pigmentary anomalies. To avoid such potential complications, “sequential combinations” of caustics were developed. Although the chemicals used were at relatively low concentrations, results showed after sequential application are the same effective as in TCA at high concentration but a lower incidence of side effects. In this way, the practitioner can control the depth reached by the caustics. Such peeling treatments are carried out in sequence in the same setting include a criopeel or a keratolytic agent and TCA 10-35%; glycolic acid, salicylic acid or Jessner’s solution are usually used as keratolytics.

Indications and contraindications are comparable to those of TCA peel at high concentration, while the side effects are comparable to those of TCA peeling at low concentration (Figure 7).

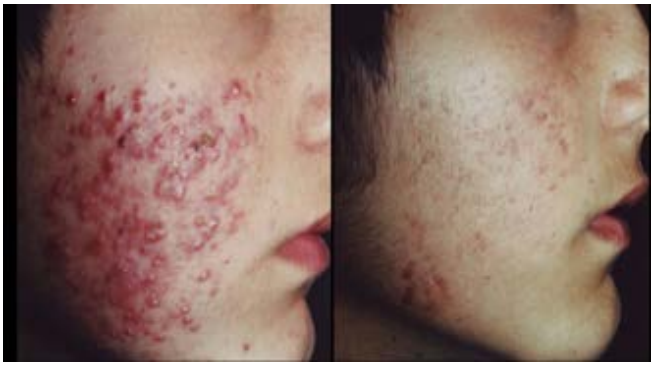

**Figure 7:** Sequential peel: Pyruvic acid + Salicylic acid.

These combinations can often be associated with other methods, such as using botulinum toxin, laser therapy, and dermabrasion [100,105,106]. To reduce the activity of dynamic wrinkles, it is recommended to use botulinum toxin before doing the peeling treatment as it can induce relaxation in the skin during the application of caustic. The laser therapy and dermabrasion [107-109], instead, should be normally preceded by peeling treatment, which must be performed on undamaged skin in order to avoid uncontrolled penetration of used substances. In some cases, skilled practitioner can perform a superficial dermabrasion before peeling treatment, in order to accelerate the spread and penetration of the caustic [110].

Sequential peels associations that are commonly used are:

1. Salicylic acid 20-30% +TCA 15-10% gel (Tosti)
2. Pyruvic acid 40% + salicylic acid 30% (Landi and Guerriero)
3. Solid CO2 + TCA 35% (Brody)
4. Jessner's solution + TCA 35% (Monheit)
5. Jessner's solution +TCA 7-15% + retinoic acid 0.4% (Fulton)
6. Pyruvic acid + TCA 10% + mandelic acid in ethanol + retinoic acid 0.4% (Landi and Guerriero)
7. Glycolic acid 70% + TCA 35% (Coleman)

These sequential associations are used for the treatment of 2 and 3 photo aging types according to Glogau classification of melanocytaria dyschromia and of mild-moderate acneic scars.

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## Chapter 5

# Hyaluronic Acid for Facial Rejuvenation

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## Abstract

The use of non-invasive techniques for facial rejuvenation is gaining popularity worldwide. There are many substances both natural and synthetic, which may be used to restore or enhance appearance and hyaluronic acid is evolving as an ideal option. Its non-allergenic state makes it a favourable and easily utilised material for injection. Hyaluronic acid has numerous beneficial properties when injected into the skin, including: hydration, space filling, lubrication, shock absorption, modulation of inflammatory cells and scavenging of free radicals. These properties enable cosmetic surgeons to use hyaluronic acid to rejuvenate the face effectively, safely and with predictable aesthetic results. There are a plethora of commercially available preparations of hyaluronic acid, each with its own clinical indications and advantages. There are also several methods of injective hyaluronic acid fillers, each depending on the area, type and nature of the defect. This chapter provides an overview of the key principles of hyaluronic acid and highlights the most important clinical principles in the use of this molecule to rejuvenate the face.

## Introduction

The popularity of non-invasive cosmetic procedures for facial rejuvenation has dramatically increased in recent years. In the United States, it is estimated that one in four cosmetic procedures now involves the use of soft-tissue augmentation with injectable fillers. In 2008, nearly 1.6 million procedures using soft-tissue fillers were performed in the United States, a 144 percent increase over the 650,000 performed in 2000 [1]. According to the Procedure Survey conducted by the American Society for Dermatologic Surgery (ASDS) in 2007, soft tissue filler injections ranked among the top 5 procedures, with soft tissue augmentation procedures showing a 130 per cent increase between 2005 and 2007 [2]. A more recent survey conducted by the American Society for Aesthetic Plastic Surgery (ASAPS), concluded that the most commonly performed non-surgical procedure in the United States was the injection of botulinum toxin-type A. The injection of Hyaluronic Acid (HA) fillers ranked fifth [3]. In 2008, more than two-thirds of soft-tissue augmentation procedures used hyaluronic

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acid-based fillers, making their use the third most performed cosmetic procedure in the United States [1].

For many years, surgical techniques dominated the facial rejuvenation process. However, in recent times practice has been moving consistently towards non-invasive cosmetic procedures thanks to both clinician choice and patient request. Indeed, non-surgical cosmetic procedures now account for the majority of all cosmetic procedures performed in the United States and in Europe. The increasing availability of such procedures and their convenience as a result of minimal 'downtime' are propelling this trend [4,5]. The use of injectable fillers for the restoration of facial volume can significantly help to rebalance facial disproportion and, by reducing rhytides and volume loss, can produce a younger and healthier appearance. Facial augmentation using soft tissue biodegradable fillers is gaining popularity worldwide as such products offer more vivid results than facial creams and chemical peels, as well as being less invasive and more subtle than facial surgery [4,5].

The first surgical soft tissue augmentation was a fat transplantation performed by Neuber in 1893 [6]. Since this first procedure, paraffin was used but was found to be associated with formation of extensive granuloma and was subsequently abandoned [7]. Pure silicone was also tried but this similarly produced severe facial distortion and latent granuloma formation [8]. Popularisation of the use of dermal bulking agents started with the introduction of the injectable bovine collagen in the early 1980s. As some patients were allergic to these products, test injections became mandatory three weeks prior to the main procedure. Recent alternative agents include acellular human dermis (Dermalogen®) and cultured fibroblasts (Isologen®); these seem to be associated with less immunological intolerance and a longer duration of action. Autologous fat, another important part of the filler armamentarium has been used extensively. However, the newer generations of fillers are becoming more favourable because the aesthetic results and duration of fat autotransplantation may be variable and difficult to manage for clinicians and patients alike. Reports on fat-grafting technique are still anecdotal and clear evidence on the 'effective take' of fat is lacking [8].

Hyaluronic Acid (Hyaluronan; HA) is a naturally occurring linear polysaccharide and is a polymer of dimeric N-acetyl glucosamine and glucuronic acid arranged in macromolecular chains [9,10]. Hyaluronic acid is naturally present in the skin as part of the extracellular matrix, is a constituent of joint fluid, the vitreous of the eye, the nucleus of intervertebral discs and the umbilical cord. Its chemical structure is well preserved across a number of species from Ascaris slime to mammals. The structure of HA is identical in all vertebrates except for subtle differences in protein and nucleic acid contaminants. The substance demonstrates no antigenic properties in any bodily tissue of any species and thus, presents a low potential for allergic or immunogenic reactions. Due to its viscoelastic properties it acts as a ground substance of the dermis. Its functions include that of space filling, lubrication and shock absorption, alongside modulation of inflammatory cells and scavenging of free radicals [11]. HA is extremely hydrophilic: hydrogen bonding between adjacent carboxyl and N-acetyl groups to the extent that it can retain up to 1000 times its weight in water, meaning that one gram of HA can bind up to 6 litres of water [12]. In the skin and in the connective tissue, the levels of HA naturally decrease with age, resulting in dermal dehydration, reduced elasticity and movement with the formation of rhytides (wrinkles), representing the rationale for the use of HA as a dermal filler [13].

HA was first isolated from bovine vitreous by Meyer and Palmer in 1934 [14]. Mammalian HA is principally synthesised by fibroblasts with the enzyme hyaluoran synthetase, which resides on the cell surface. Formed HA is then extruded via the cell membrane into the extra-cellular space. Commercially available preparations of Hyaluronic acid are usually

produced through extraction from rooster combs or by recombinant production from different strains of *Streptococcus bacterium* (e.g., *Streptococcus zooepidemicus*), each with unique rheological properties [15]. Endogenous HA has a half-life of approximately 24 hours, before it is enzymatically broken down by hyaluronidase and free radicals, followed by hepatic degradation to water and carbon dioxide [16]. The naturally occurring break down of HA by hyaluronidase represents an important feature of the HA fillers, as well as a major advantage over the collagen fillers, because HA which is injected excessively, in a superficial plane or inaccurately can easily be treated by intralesional injection of hylauronidase. Commercially available preparations of hyaluronidases are available and principally used to treat over-injection of hyaluronic acid [17].

Research and development in Hyaluronic Acid (HA) has crossed many areas of biomedicine. The therapeutic utilisation of hyaluronic acid started in ophthalmic surgery and progressed to orthopaedic surgery, as an adjuvant lubricant for joints in patients with osteoarthritis [18]. The use of HA was brought to the attention of plastic surgeons via tissue engineering routes. It was extensively researched with a view to the production of dermal regeneration templates for reconstructive surgery. There are a considerable number of on-going research projects dedicated to HA, with significant international collaborations.

The duration of the cosmetic effect of injected HA is determined primarily by its susceptibility to enzymatic degradation by the fibroblasts, resulting in the formation of shorter HA chains, which are then ingested by macrophages and keratinocytes. Supplementation of HA injection with oral antioxidants theoretically increases the duration of HA fillers but this has not been proven. In order to reduce its solubility and produce a more viscous and stable compound that can remain in the skin for longer, HA has been progressively bioengineered (principally through alcohol esterification) to form more stable polymers with higher resistance to enzymatic degradation. Bioengineered HA retains its biocompatibility but allows for a prolonged dissolution rate and an increased half-life [5]. Furthermore, the degree of esterification and cross-linking can be varied to alter its viscosity and thus, expands the range of cosmetic uses. The viscoelastic property of HA is determined by the length of the molecular chain, the concentration, the cross linking and the particle size.

Commercially available HA fillers are differentiated by many features, including their particle size, type of crosslinking agent, degree of crosslinking, percentage of cross-linked HA and the amount of free (un-modified) HA present. All these physical and chemical properties will influence the clinical characteristics of each type of HA filler and impact on clinical indications, ease of injection, degree of tissue filling, longevity, post-treatment appearance and side effects. HA have many natural advantages over other commercially available soft-tissue fillers, including: biocompatibility, non-antigenicity/immunogenicity, non-toxicity, ease in administration, low cost and reversibility. Further to this, it has a good safety profile with predictable results and requires minimal recovery time.

## Indications

The hallmark of the aging face is the loss of subcutaneous volume. This is commonly associated with increase in facial vasculature, alterations in pigmentation, increases in number and depth of lines and rhytides of the skin and decreased tissue elasticity and hydration. Histologically, this is associated with a thinning of the epidermis and dermal atrophy with loss of elastic tissues and dermal collagen. Aging adversely affects the skin by reducing viscoelasticity and dermal volume, resulting in the formation of rhytides. HA dermal fillers have a role in addressing these deficits and may be used alone, or in combination with other nonsurgical products such as botulinum toxin or operative interventions [5,19]. The treatment for age related facial changes can be multiple, encompassing skin care products,

energy based therapies (lasers, light sources, radiofrequency, etc.), fillers and toxins. HA fillers play a major role in the correction of changes associated with aging, especially those of the mid and lower half of the face, including cheeks, peri-orbital regions, naso-labial folds, vertical lip lines, marionette lines around the mouth and lips as well as the lips themselves. The concept of the ideal filler has been debated for years. A filler should be easy to inject, long lasting, well tolerated and without any adverse reaction. To date, the HA fillers are the only injectable products that fulfil the majority of these criteria. The indications for hyaluronic acid injection are summarised in Box 1.

| |
|---|
| • Loss of vermilion bulk and projection (pout) |
| • Loss of lip fullness |
| • Loss of lip eversion |
| • Volume replacement of marionette line |
| • Volume replacement of the deep mental groove |
| • Volume replacement of the anterior jowl line |
| • Blunting of nasolabial folds |
| • Malar atrophy |

**Box 1:** Indications for hyaluronic acid injection.

The primary indications for HA fillers are volume enhancement for photo-aging rhytides, deep nasolabial folds, lip rhytides, marionette lines, lip filling and contouring, chin and cheek augmentation and treatment of tear trough lines. Generally HA is not ideal for superficial rhytides, instead it is more suited for deep folds and volume augmentation. However, smaller molecular preparations have been shown to have good effect with superficial rhytides. After a full pre-treatment assessment and pre-treatment photographs, the correct product should be selected. The greater the viscosity of the gel, the better its ability to resist shear and exert a deformational force on surrounding tissue to correct a defect. The pay-off for such qualities is palpability and firmness to touch. Superficial injections have, as expected, a higher risk of visibility. This has led to various HA products being used for different areas of the face due to difference in residence time, persistence, injectability and the need for local anesthetic. The differences between the various HA agents are due to the source derivation (animal vs bacteria), cross-linking (the method used to create cross linking and the degree of cross linking present), the concentration of HA, the amount of free HA (non-cross-linked) and the particle size and uniformity of structure [20]. Different manufacturing processes result in varying firmness of the gel and so different amounts of swelling caused by the accumulation of water. As a result of this variability, a wide range of HA fillers are now commercially available and particular fillers have a better theoretical application to different parts of the face (Table 1). For example, a viscous filler with a larger 'granule' size would be best suitable for injecting into the cheeks more than a lip because of its risk of palpability (Figure 1).

| Preparations | Company | Indications | Duration of Effect | Advantages | Disadvantages |
|---|---|---|---|---|---|
| Hylaform®/ Hylaform Plus® | Genzyme | Moderate to severe facial lines and rhytides | 3-4 months | Good safety profile<br>No skin test necessary - can be used at the initial consultation | Results may be short-lived, lasting approximately 3 months.<br>Cannot be used in patients with hypersensitivity to avian proteins (eggs).<br>With Hylaform plus, superficial injection may lead to skin discolouration |

| | | | | | |
|---|---|---|---|---|---|
| Restylane®/ Restylane-L® | Medicis Aesthetics | Moderate to severe facial rhytides and folds, nasolabial folds or parentheses lines<br>Lip augmentation | 6-12 months | Good safety profile<br>Predictable results<br>No skin test necessary - can be used at the initial consultation<br>Relatively long duration of effect<br>Easily injected through small-gauge needles<br>Restylane-L contains lidocaine local anaesthetic | Rare immunologic reactions<br>Higher incidence of bruising, pain, and post-procedure swelling<br>Relatively expensive |
| Perlane®/ Perlane-L® | Medicis Aesthetics | Moderate to severe facial rhytides and folds, nasolabial folds or parentheses lines | 6-12 months | Good safety profile<br>Predictable results<br>No skin test necessary - can be used at the initial consultation<br>Relatively long duration of effect<br>Perlane-L contains lidocaine local anaesthetic | Rare immunologic reactions<br>Higher incidence of bruising, pain, and post-procedure swelling<br>Relatively expensive |
| JUVÉDERM® Ultra | Allergan, Inc | Juvéderm® ULTRA 2 for superficial facial lines around the lips, corners of the eyes<br>Juvéderm® ULTRA 3 for nasolabial folds and lip augmentation<br>Juvéderm® ULTRA 4 for deep facial folds and rhytides<br>Juvéderm® ULTRA SMILE for lip augmentation and fine perioral rhytides<br>Juvéderm® HYDRATE restores hydration to the face, neck, décolletage and hands | 3-12 months | Good safety profile<br>Predictable results<br>No skin test necessary - can be used at the initial consultation<br>Lidocaine 0,2% (no in Juvederm® Hydrate) | Only short term complication results are available<br>Rare immunologic reactions |
| JUVEDERM® Vycross™ technology | Allergan, Inc | Juvéderm® VOLUMA® for volume restoration of the cheeks, cheekbones, and chin<br>Juvederm® VOLIFT for severe facial wrinkles and folds<br>Juvederm® VOLBELLA for the lip area and fine lines | Up to 18 months<br>Up to 12 months | Lidocaine 0,2%<br>Good safety profile<br>Predictable results<br>No skin test necessary - can be used at the initial consultation | |

**Table 1:** Hyaluronic Acid Fillers [13,23,24].

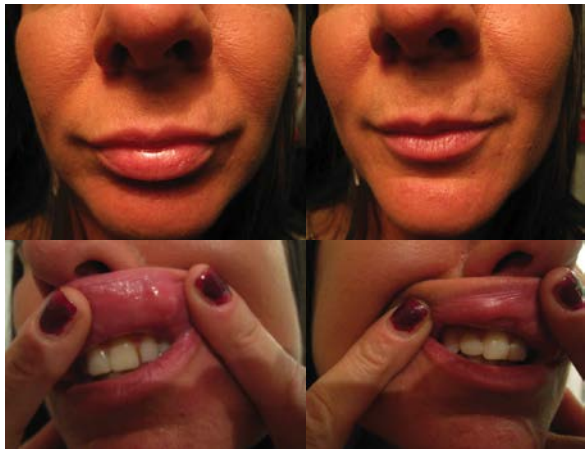

**Figure 1:** Granulomas following injection of thick viscous filler in the upper lip.

A new generation of dermal filler is now available and it is characterized of new technology: vycross™ (Allergan, Inc, Irvine, CA). Its patented Vycross™ technology incorporates short chain HA together with long chain HA to provide more efficient crosslinking than other dermal fillers [21].

In Vycross™ dermal fillers the more efficient crosslinking results as a longer product duration and the elastic modulus (G' or gel hardeness) of ~160 Pa is lower than that of other fillers, [22] this provides a smoother and softer gel that is easy to inject.

Conversely, a softer product with a smaller particulate size would not give the volume enhancement needed in the deep tissue planes. It is for this reason that practitioners should be familiar with the range of products so that bespoke treatment may be offered to the patients, tailored to individual need. See Box 2 for a summary of some of the factors involved when choosing an appropriate HA filler.

| | |
|---|---|
| • | Concentration of hyaluronic acid |
| • | Type and degree of cross-linking (solubility) |
| • | Ratio of cross-linked to non-cross-linked molecules |
| • | G prime (stiffness) |
| • | Duration of action |
| • | Design and size of the syringe |
| • | Presence of lidocaine |
| • | Cost |

**Box 2:** Factors to consider when choosing a hyaluronic acid agent.

## Pre-Treatment Evaluation

Pre-treatment evaluation requires a comprehensive knowledge of the filler materials available and the potential treatment effects, an understanding of the aetiology of rhytides and an appreciation for patient expectations. Fine, superficial rhytides better respond to therapy at the intradermal level. Deep, substantial rhytides typically have a subcutaneous or muscular component and are better corrected through subcutaneous filling. Often a rhytide will have both a superficial and deep component, such as the naso-labial fold, and both of these components need to be addressed to obtain optimal results [5]. The identification of patients' expectations is a key element and should include prior experience

with fillers, their understanding of the longevity of the treatment and the necessary time for recovery. Patients of all ages are selecting soft tissue augmentation, either as a precursor to or a substitute for cosmetic facial surgery, but there is a trend toward the use of injectable devices in younger patients (aged 35-50 years) for facial rejuvenation.

Each patient has a different treatment needs, ranging from correction of fine lines and rhytides in younger patients to primary volume restoration in older patients and their needs must guide the treatment approach. Practitioners should aim to advise patients in the selection of the most appropriate rejuvenating treatment based on a variety of factors, specifically, patient age, motivating factors, timing, cosmetic area to be addressed and desired outcome. A series of steps need to be determined to formulate the most appropriate approach for volume restoration with injectable devices for satisfying patient treatment expectations.

Cosmetic medicine has developed rapidly over the years as a better understanding of the process of facial aging has led to a more targeted and efficient treatment approach. Facial aging is now established to be due to a number of different features. These include the involutional loss of dermis, resulting in loss of skin tone, gravitational changes due to loss of elasticity, remodelling of bony and cartilaginous structures, and sun damage causing photo-aging. More recently, the concept of volumetric loss in the face has further added to our understanding; fatty volume either migrates or is lost from the face. This occurs in predictable areas and a number of treatments now specifically address this issue either alone, or in combination with traditional rejuvenation techniques. Some of these factors are preventable - most notably the sun damage to the skin that alters dermal composition - but others are less so; gravitational changes are dependent on the environment and volumetric loss is somewhat unavoidable and largely determined by genetic variables. The overall effect of these processes gives us the features of the aging face; flattening of the forehead, brow, glabella and temporal concavity in the upper face, descent of the nasal tip and flattening of the cheek in the mid face and recession of chin, appearance of jowls, loss of lip fullness, and descent of oral commissures in the lower face. In addition the aging process is manifested in the form of rhytides throughout the face. Surgical procedures address laxity within the tissues and reposition the soft tissue of the face, on a 'macro' scale. Additional 'micro' adjustment can be made with fat transfer at the time of surgery, the so-called 'volumetric' facelift. Independent surgical fat transfer is still useful but does involve a hospital or clinic stay, and is quite clearly an invasive procedure. However, surgical fat transfer does not address the finest lines in the face. Rhytides caused by active muscle contraction can be ameliorated by the use of botulinum toxin. For established lines there is anecdotal evidence that repeated use of this modality may allow the reversal of superficial lines, although formalised studies into this are limited. There is also a trend amongst the younger population to undergo botulinum toxin treatments in order to prevent the formation of rhytides, particularly in the forehead area. That said, most treatments for established rhytides are aimed at volumetric replacement of soft tissue: dermal and/or deep tissue plane augmentation. As previously outlined, the ideal filler substance should be non-allergenic, non-carcinogenic, with minimal adverse sequelae, no associated migration and minimal inflammatory response. It should be reproducible, durable, simple and painless to administer, with minimal recovery time, user-friendly, easily stored and large amounts should be readily available. It should preferably have a long-lasting effect with slow degradation in the body.

There are advantages to temporary (rather than permanent) fillers; if the result is not to the patients liking, then it will be reversed over a period of time. Permanent fillers, while an attractive proposition, have two obvious drawbacks; misplacement of filler usually necessitates surgical removal, and the filler placement cannot subsequently be adjusted to

account for ongoing age-related changes in the face. Finally, physicians must gain informed consent by counselling patients regarding the associated risks and benefits of injectable substance therapy [24].

## Pearls

The injection of HA is generally carried out in the outpatient clinic setting, with the patient in an upright position for gravitational rhytides to be visible, with the head supported on a headrest to avoid sudden movements. Patients on anti-platelets or anti-coagulants are advised regarding the higher risk of bleeding and advised to stop such agents prior to procedures.

Anesthesia, where applied, is usually in the form of topical creams but injection local anaesthetic or nerve blocks may be required, especially for lip procedures which can otherwise be quite painful.

Using a 27-30 gauge needle, the agent is injected into the middle to deep dermis, except in the red lips where it is more commonly injected intramuscularly rather than intradermally. Larger molecular HA will require larger gauge needles for injection. If injected subcutaneously the material is wasted as its bioavailability is very short due to quicker enzymatic degradation and the effect may be limited. The senior authors' current practice involves using a layering technique where heavier gels are injected into the deeper layers and lighter gels into the superficial layers. Constant movement of the needle is important in producing an even distribution of product, and avoiding intravascular injection [25]. Injection above the periosteum is favourable as it produces re-inflation of the natural fat pads, in the brow, malar, buccal, and mental areas. After injection, the area should be massaged by the practitioner (not the patient) to smooth out any irregularities. Care should be taken to avoid migration of the filler into an undesirable location. Ice packs may be used to decrease swelling and pain and the patient is advised to minimize movement of the injected area for the next couple of days, in order to reduce the incidence of bruising. Some physicians also advise abstinence from alcohol in the immediate post-procedure period, but evidence to support this is limited. Avoiding sun exposure within the first week may reduce the risk of skin redness and inflammation.

Combining HA filler treatment with injection of botulinum toxin is becoming increasingly popular because it extends the cosmetic response of the HA agent by immobilising the muscles and thus, increasing the biodegradation time. However, research is limited on the subject of concomitant injection and some authors prefer to inject botulinum toxin and fillers with a delay of at least one week, performing the former first.

Depending on the filler agent used and the depth at which it is injected, the effects of soft tissue augmentation will last from 4 to 12 months. It is difficult to be accurate in predicting the duration of effect and patients should be advised of this. However, a few guidelines may be reasonably mentioned. Most injections last at least three months and often up to six months, although there are anecdotal reports of longer duration and, indeed, some of the newer products claim up to 18 months of activity. On balance, it is probably best to advise patients to expect 4-6 months efficacy, and that treatments may be needed 2-3 times per annum. Concomitant treatment with botulinum toxin may prolong these effects [5]. There is some suggestion, although not proven as yet, that the repeated application of HA in the same area does, in fact, eventually provide a long-lasting result; whether this is due to the sustained increase of extracellular matrix, or whether this is the result of repeated scarring is not known. However it is to be point out that interval treatment times are dependent upon patient's needs and perception of the cosmetic lasting effect; moreover, financial

considerations should be contemplated. Many patients who claimed to be happy with their previous surgeon still chose to move to a different practice for a variety of reasons unrelated to their previous practitioner.

## Technical Points

Anaesthesia is often obtained using a combination of topical, local and regional anaesthetic agents. Topical anaesthetic creams (benzocaine, lidocaine) should be applied 20 minutes before injecting local anaesthetic. Infra-orbital and mental nerve blocks provide the mainstay of regional anaesthesia. Local anaesthesia is usually delivered to the peri-oral area. More recent HA injectable filler are commercialized with local anaesthetic combined with the filler substance within the same syringe reducing discomfort for the patients and offering time effectiveness for the practitioners [5,13].

The depth of the filler injection is the key factor in obtaining an effective aesthetic result. Small-particle hyaluronic acid fillers (i.e.: Restylane, Juvaderm Ultra 2 and 3) are suited to injection into the superficial dermis and are ideal for correcting superficial rhytides, such as those of the forehead, periorbital and perioral regions. Hyaluronic acid with large-sized particles (i.e: Hylaform Plus, Juvaderm Ultra 4 and Voluma) is best used in the mid-dermis for the glabellar region, nasolabial folds and for atrophic scars (Figure 2). Layering fillers at different depths can improve the overall aesthetic result. These are the most commonly used techniques:

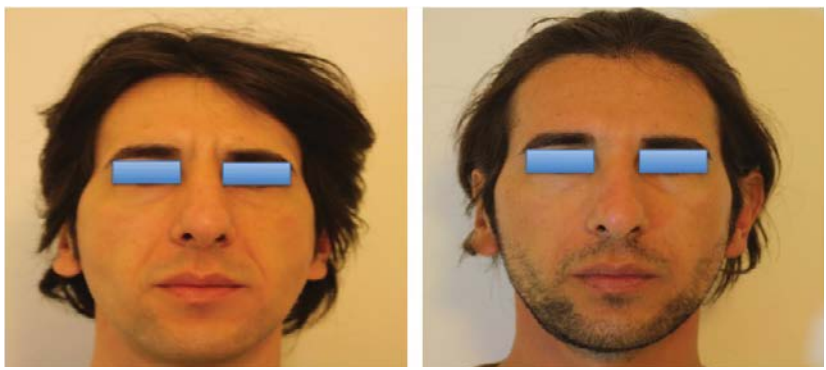

**Figure 2:** On the left pretretment frontal view- On the right one year post treatment on the nasolabial folds (Juvederm® VOLIFT).

### Linear threading

With this technique the fold is filled by a single puncture to the epidermis and injecting the HA agent along the track of the needle producing linear volume. The full length of the needle is used to create a channel in the middle of the rhytide or fold. The filler material is injected as the needle is slowly pushed forward so that the material is deposited along the entire length of the rhytide or fold. A retrograde injection technique may also be used, whereby the material is injected while the needle is being retracted. This technique is best used for the treatment of white-roll lip border and the nasolabial fold and it is the commonest technique used by the first author.

### Serial puncture

With this technique the fold is filled by multiple injections of the agent, all in a row. This technique involves serial injections along the fine rhytide or fold. The injection site should

be in close proximity such that the injected material congregates into a smooth, continuous line. No spaces should remain between the serially injected filler. This technique is optimal for the glabellar, philtral column enhancement, nasolabial folds and fine rhytides. It is commonly used in the periorbital and perioral areas by the first author.

### Fanning

With this technique, the epidermis is punctured once, and then the needle is fanned out while injecting the agent, producing volume in a triangular shape. This is similar to linear threading, but before the needle is withdrawn, its direction is changed and a new line is injected. The fanning pattern of lines should be evenly spaced in a progressive clock-wise or anti-clockwise direction. This will result in an even filling and shaping. This technique is best used for deep malar injection.

### Cross-hatching (Cross-radial)

With this technique multiple injections of linear threading can be combined within crisscross directions at right angles to provide volume in a square shape. In this technique, again the needle is inserted in a similar way to linear threading. A series of linear threading injections is made in the treatment area. The pattern of lines should be evenly spaced in a progressive grid so that the contour is evenly filled and shaped. This is analogous to fat transfer techniques and it is performed by the senior author for deeper volumetric adjustment. This technique is best used for the oral commissures, facial contours and the perioral area.

### Fern pattern

This involves serial puncturing in a linear manner but is done perpendicular to the actual fold on either side of it, increasing dermal stiffness. This technique can be performed safely and effectively in the periorbital regions [26].

### Topical hyaluronic acid

Topical HA is not cross-linked and it is therefore easily absorbed. It was first used as a vehicle for the delivery of other drugs to the skin, being particularly useful for sustained release and localized delivery. As the significance of HA in water retention in the dermis has come to light, topical pure HA has become a cosmetic product in its own right. In the superficial epidermis, it acts as a humectant contributing to moisture content and decreasing trans-epidermal water loss. Once absorbed into deeper dermis it increases turgidity within the dermis. It also assists in proliferation of dermal fibroblasts, promoting extracellular matrix production *in vitro*, although there is no clear evidence this occurs *in vivo*. Since non-cross-linked HA has a short half-life, this will need frequent application. As it may increase the water retention of the dermis, it is marketed as a plumping agent for the skin. It is worth noting that the potential benefits of topical hyaluronic acid are theoretical and at the time of writing the authors are not aware of any objective studies in this area and so cannot recommend its use.

## Post-Treatment Care

The surgeon should immediately massage the injected area rather than the patient performing the massage. Cooling packs may help to prevent post-injection bruising and oedema. The patient's head should be elevated by thirty degrees for the first 24 hours. Oral anti-histamines can be prescribed to reduce post-injection oedema and are especially useful in those with previous adverse reactions to dermal fillers [1,5]. Sun exposure,

physical activity, alcohol intake should be avoided in order to reduce the risk of developing complications in the early post-treatment phase (up to seven days).

## Complications

The most common adverse reactions to HA are due to the cross linking process used rather than the HA source or nucleic acid contaminants, though the exact reason for the reactions is still unclear [8,25]. In general, hyaluronic acid fillers have an excellent safety profile. Many complications can be avoided with careful injection technique or reversed by injection of hyaluronidase [1]. The most commonly reported complications include local bruising, purpura, erythema, tenderness, pruritus, oedema and hypersensitivity reactions irregularities secondary to nodule formation and delayed inflammatory reactions (Box 3) [5]. These are seen in up to 12% of patients. The incidence of these complications is much less frequent compared to injectable collagens and equally the volume of HA agent required is significantly less than that of collagen. Serious complications such as hematoma formation and significant swelling are reported to occur in up to 1:1600 cases. Rare side effects such as sterile abscesses, induction of sarcoid and even angioedema have also been reported [8,27].

- Local bruising
- Purpura
- Erythema
- Tenderness
- Pruritus
- Oedema
- Irregularities secondary to nodule formation
- Immediate hypersensitivity reaction
- Delayed hypersensitivity reaction

**Box 3:** Complications of hyaluronic acid injection.

The surgeon should inform the patient that swelling may last up to 3 weeks but will usually last 1-2 days. Similarly, the lips may appear overcorrected due to swelling in the early post-injection period. Bruising may last over one week but can be ameliorated by cessation of aspirin and NSAIDs taken at least two weeks before the injection. Asymmetric animation may occur due to the residual effects of the local anaesthetic. All patients should be seen within two weeks after treatment. Hyaluronidase injections and massage may help to correct irregularities that are picked up during follow-up.

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## Chapter 6

# Calcium Hydroxyapatite and Poly-L-Lactic Acid: The Long Lasting Fillers

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## Abstract

During the times several dermal fillers have been introduced in the market. Theoretically, The ideal soft-tissue filler substance for wrinkles and skin defects should be safe, biocompatible, stable after implantation, nonmigratory, resistant to phagocytosis, and pliable, and should persist and maintain its volume without being absorbed or degraded. It should induce minimal foreign body reaction, including granuloma formation; be nonteratogenic, noncarcinogenic, noninfectious, and nonallergenic; not require pretesting; painless, and inexpensive; and able to be stored at room temperature. Unlikely, this kind of filler still does not exist, however there are 2 products that are able to give a long lasting results, without the side effects, already known, of permanent fillers. In this chapter, use, mechanism of action, potential complications and the injection technique of Calcium Hydroxyapatite (CH) and Poly-L-Lactid Acid (PLLA) dermal filler's are exposed.

## Introduction

Beginning in the 1970s, dermal filler substances consisting of highly viscous fluids or polymer particle suspensions were injected beneath wrinkles and acne scars [1-3]. These substances are useful for the correction of congenital or traumatic facial, bony, and soft-tissue defects, etc.; and currently may be grouped according to the degree of degradability [4]. In general, fillers can be grouped as biodegradable and non-biodegradable (permanent) products. Biodegradable materials such as collagen, hyaluronic acid, hydroxyethyl methacrylate, dextran, and polylactic acid are removed by phagocytosis over a period of 3 to 24 months, depending on the amount and type of bulking agent implanted [5]. Permanent fillers such as paraffin, fluid silicone, Teflon, or silicone particles have an irregular surface that cannot be phagocytized and may eventually form foreign body granulomas because of the memory of macrophages and giant cells (so called frustrated macrophages) [6]. Particles and microspheres smaller than 15 micron are generally phagocytized and can be transported to local lymphnodes. Larger microspheres from non- resorbable polymers with a smooth surface are encapsulated with fibrous tissue and escape phagocytosis. Clinically, all injected fluids and particles have been shown to cause foreign body granuloma in a small percentage of patients [7-9]. Until the mechanism of granuloma formation is fully understood, the chance of its late development is not predictable. The ideal soft-tissue

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filler substance for wrinkles and skin defects should be safe, biocompatible, stable after implantation, nonmigratory, resistant to phagocytosis, and pliable, and should persist and maintain its volume without being absorbed or degraded. It should induce minimal foreign body reaction, including granuloma formation; be nonteratogenic, noncarcinogenic, noninfectious, and nonallergenic; not require pretesting; painless, and inexpensive; and able to be stored at room temperature [10]. Although the ideal filler has not yet emerged, there is an ever-increasing body of data demonstrating the search for filler that meets these demanding criteria. The clinical persistence of an injectable material and its effect on facial volume restoration depends in part on the amount, depth, and shape of the implant. A thin strand applied beneath a constantly moving wrinkle is absorbed faster than a round depot in the skin of the forearm or a rat's forehead. The carrier substance, whether fast or slowly resorbable, may play an important role on persistence as well. Host defense mechanisms react differently to the various filler materials, but all substances-resorbable or nonresorbable-appeared to be clinically and histologically safe, although all may exhibit undesirable rare clinical side effects [11]. Because the mechanism of late inflammation or granuloma formation is still unknown, early histologic findings are not useful in predicting possible late reactions to filler substances. These can only be verified in exact clinical long-term studies and in an independent centralized European and/or U.S. independent implant registry. Currently there are 2 fillers named as semi-permanent: one of calcium hydroxyapatite, and another of Poly-L-Lactic Acid.

## Calcium Hydroxyapatite

Calcium Hydroxyapatite (CH), the main mineral component of bone and teeth, is a naturally occurring substance found in humans, making it compatible and contributing to its nonantigenic properties. Radiesse (Merz Aesthetics, Palo Alto, CA) is an injectable filler material composed of synthetic Calcium HydroxylApatite (CaHA) microspheres suspended in an aqueous carrier gel. Seventy percent of the composition of Radiesse is sodium carboxymethylcellulose carrier gel; the remaining 30 percent of the composition is CaHA microspheres. These uniform microspheres (25-45 microns) are identical in composition to the mineral portion of human bone and teeth [12-14]. It should be stored at room temperature (15°C to 32°C) and expires 2 years from the date of manufacture. The formulation allows 1:1 implant-to-tissue volume defect correction and minimizes the need for overcorrection. Results from extensive in vitro and in vivo safety studies, including toxicology assessments, standar- dized biocompatibility testing, and a three-year animal study, demonstrate that injectable CH is biocompatible, nontoxic, nonirritating, and nonantigenic [12]. Because CH contains no animal or human tissue derivatives, patient sensitivity testing is not required before use [15]. In the United States, injectable CaHA has been used for several years for correction of oral and maxillofacial defects, vocal fold augmentation, and as a radiographic tissue marker [16]. Treatment sites amenable to CH injection include the naso-labial folds, marionette lines, prejowl sulcus, zygoma and malar eminence, tear trough depressions, nose, chin, acne scars, and it is also FDA-approved for facial augmentation in HIV patients with facial lipoatrophy [17]. Lips augmentation with CH filler has been advocated by some authors, however the high percentage of nodules occurred in this site don't make this filler suitable for this indication [18]. CH fillers provide immediate correction, and following injection, the gel carrier is absorbed over several months. The CH microspheres left behind from a scaffold for ingrowth of fibroblasts. New collagen fibers are formed, which anchor the microspheres in place and prevent the migration of the implant. The microspheres gradually dissolve and are broken down to its metabolites, calcium and phosphate ions, over a period of several months to years [19]. Usually less volume is required with Radiesse to produce the desired correction as compared with hyaluronic acid fillers. The longevity of CH fillers

seems to depend on several factors, including the site of injection, the injection technique, and the patient's metabolism of the product; however the durability of the correction persist for 9 to 18 months and can last longer if deposited in areas of minimal facial mobility [17].

## Mechanism of Action

After injection, the carrier gel is gradually absorbed, and the CaHA particles remain. A local fibrobroblastic response at the site results in collagen matrix encapsulation of the CH particles, similar to a grapevine growing through a garden trellis. The result is a highly biocompatible long-lasting implant with similar characteristics to adjacent tissue [19]. Thus, when CH is implanted in soft tissue, new soft tissue develops. No calcification or osteogenesis has been reported in the extensive literature describing the use of CH in a variety of soft tissue applications [20,21]. A study of dermal tissue biopsies after injection of Radiesse, light microscopy, and electron microscopy at one month postinjection revealed the presence of CH microspheres, with minimal or no inflammatory response or fibrosis. Histological and immunohistochemical analysis studies have shown a local histiocytic and fibroblastic response resulting in new collagen production around the microspheres [19]. Primarily, type I collagen and a small amount of type III collagen were found within the infiltrating fibrovascular stroma, consistent with the process of remodeling. Electron microscopy studies demonstrated an increase in histiocytes and associated fibroblasts, which appear to anchor down the microspheres and encourage new collagen formation. The persistence of microspheres and new tissue formation observed was accompanied by evidence of clinical improvement at six months. From a safety perspective, it is important to note that there was no evidence of granuloma formation, ossification, or foreign body reactions at one or six months [17].

## Injection Technique

Because of the relative viscosity of CH, a 27 or 28 gauge needles is recommended. It should be injected in a retrograde fashion using a linear, threading, fanning, and/or cross-hatching technique, depending on the area being treated. Injection volumes vary with the treatment site. Generally, a lesser volume of CH is required to provide the same degree of correction as hyaluronic acid.

CH should ordinarily be injected at the subdermal plane, especially when filling creases, wrinkles, and deep lines. Injection depth can be just in the subcutaneous space but superior to the periosteum. The injection can also be placed on the periosteum if the intent is to augment the facial bony skeleton. Placement on the periosteum will not stimulate bone growth in the area. Correction is approximately 1:1 and is apparent immediately upon injection. Overcorrection is not necessary, nor is there a need to build correction over multiple sessions. When injected, patients usually claim a bit of pain for a few, which can be reduced adding lidocaine to the filler before the injection. The injection can be made both with a needle or a micro-cannula, however more often, compared to other fillers, the needle can be occluded by CH, if this occurs, needle must be changed. At the end of the procedure, the injected area is quite hard to touch due to the product; this will be felt by the patient for about 3 days. Less oedema can be observed at the site of injections the day after, comparing to jaluronic acid filler. Immediately after injection, the site should be gently massaged and molded by the treating physician to help ensure a smoother implant. Patients can massage the injected area the first days after the injection to quickly reduce the hardness of the product felt by the patient-self. Post-treatment care involves, as for the other fillers, application of ice over the injection areas to reduce and limit tissue edema and ecchymosis.

## Potential Complications

CH filler enjoy an excellent safety, with adverse events reported typical of that observed with other short-acting fillers such as hyaluronic acid. The potential for serious adverse reactions with Radiesse appears to be low. There is no evidence of granuloma formation occurring with CaHA [17]. Although the presence of nodules visible through the skin has been reported, these nodules are technique related due to too superficial injection of CH or inappropriate use of CH. If such nodules occur, they can be easily reduced using aggressive massage techniques [17].

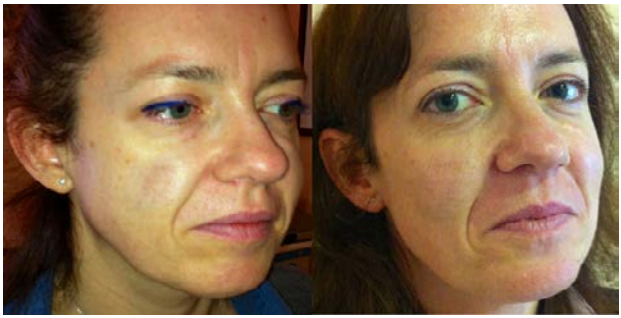

**Figure 1 & 2:** Pre-op and post op of a patients treated for aging and zigomatic volume replacement with 1,5 mL of Radiesse.

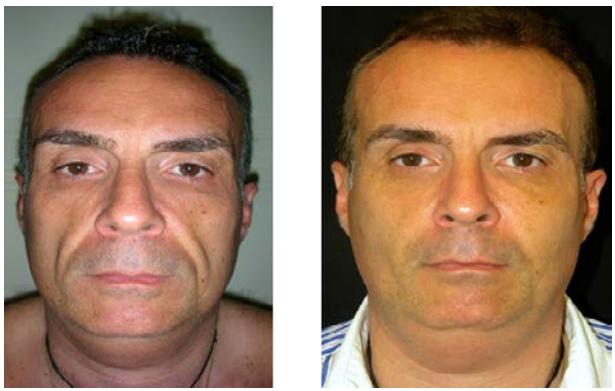

**Figure 3 & 4:** Pre-op and post-op of an HIV+ patient affected by facial lipoatrophy, treated with 12 mL of Radiesse.

## Poly-L-Lactid Acid (PLLA) Filler

Injectable PLLA is a new class of synthetic devices that provides a semipermanent option to correct facial volume loss. Filler based composed of PLLA is named Sculptra in the U.S.; Sculptra was approved with CE Mark certification under the trade name New-Fill in Europe. The stimulatory action of PLLA is one of the main characteristics that differentiate it from other fillers. Most other filler, such as hyaluronic acid, have a passive and direct effect on enhancing volume. Their augmentation is limited to the persistence of the filler material and, once degraded, further injection is required. Likewise, the augmentation effects of PLLA tipically require multiple injections and are delayed in nature. But the new collagen deposition yields results that last long after the injected material is absorbed [22]. Sculptra

obtained US Food and Drug Administration approval in 2004 for use as soft-tissue filler into lipoatrophy of cheeks and temples of human immunodeficiency virus patients who are under highly active antiretroviral therapy [22,23]. Polylactic acids do not occur naturally, but were synthesized by French chemists in 1954. Polylactic acid and polyglycolic acid have been used safely in suture materials (Vicryl, Ethicon, Inc., Piscataway, NJ); in resorbable plates and screws; in guided bone regeneration; in orthopedic, neurologic, and craniofacial surgery; and as drug delivery devices [22]. Sculptra is composed of microparticles of PLLA, a biocompatible, biodegradable, and synthetic polymer from the alpha-hydroxy-acid family. The final composition of Sculptra consists of 150 mg of PLLA, 90 mg of sodium carmellose, and 127.5 mg of apyrogenic mannitol in the freeze-dried form. The PLLA particles provide the durable attributes of sculptra treatment. Raw material is milled, sieved, and sterilized before manufacture. PLLA microparticles are irregular in shape and have an average particle diameter of 40-63 micron. Polylactic acid is synthesized by esterification and polymerization of lactide monomers where the material is immunologically inert [24]. The amorphous crystalline structure and high molecular weight (>100,000 Da) of the product are responsible for the slow absorption when injected into the tissue. Once injected, 75 percent of the PLLA is broken down into CO2 and H2O. No allergy testing is required before use since PLLA is a synthetic material of nonanimal origin [22].

## Mechanism of Action

The mechanism of action of PLLA is based on its ability to stimulate fibroblast proliferation and neocollagenogenesis. However, his mechanism of action by which PLLA corrects facial volume deficiencies is not comprehensively understood. It is postulated that this is due to a foreign body reaction to the injected material, which stimulates a cellular inflammatory response. The resultant formation of a vascularized, connective tissue capsule ensues, which is eventually composed of fibroblasts and new collagen deposits. The breakdown of PLLA occurs by hydrolysis into lactate, which is eventually converted to pyruvate, and oxidized into carbon dioxide for release [22,24].

Several histological studies of PLLA injections in mice reported a pronounced tissue response. Investigators observed polylactides surrounded by vascularized connective tissue capsules, consisting of connective tissue cells with mononuclear macrophages, lymphocytes, foreign body cells, and mast cells after one month of implantation. Over time, the capsule surrounding the implants decreased in cell number, whereas thickness and collagen fibers increased. In general, PLLA was well tolerated by the tissue and no acute inflammation, abscess formation, or tissue necrosis was observed adjacent to the injection sites [25]. Sculptra induces an immediate, local reaction that is followed by a progressive increase in volume. Within a few days, water absorption and the reduction of edema will result in a return to the baseline depression. Within several weeks of the injection, a natural, soft increase in dermal thickness due to neocollagenogenesis will begin to take shape.

## Reconstitution and Injection Technique

PLLA filler, before its use, must be reconstituted with sterile, bacteriostatic injectable water (5 to 8 mL; the more water is used, the less possibility of papules or nodules you have); sufficient time to reconstitution is paramount, usually 24/48 hours. Inadequate mixing of PLLA with water leads to inadvertent injections of clumps of dry micro-particles, increasing the risk of nodule formation when they hydrate in vivo.

For uniform hydration, do not agitate but allow the powder cake to absorb the sterile $H_2O$ slowly overnight. When the water is added, it will take about five minutes for the powder to dissolve. The mixture is then kept overnight for complete hydration. The now reconstituted

product is stored at room temperature to achieve proper viscosity for injection. It is fine to swirl, agitate, or shake hard after hydration overnight. The vial is thoroughly agitated before use. It is optional to add 1 mL of 1 percent lidocaine or lidocaine with epinephrine immediately before injection, making it slowly drip through an 18-gauge needle. When added too quickly, lidocaine can precipitate the hydrogel suspension, leading to difficulty, such as clogging, while injecting. The suspension of PLLA is injected with a 1-cc Luer-lock syringe with a 25-gauge needle to provide less clogging, more clogging results with the use of a 26-gauge needle. It is important for the injector to assess the viscosity of the suspension before insertion of the needle into the skin to deliver the product. Injection of the material is performed while slowly withdrawing the needle. Most importantly, injection of product must be stopped before withdrawal of the needle so that no product is injected superficially. This will decrease the risk of papule formation. PLLA is injected in the deep dermis and subcutaneous junction in one of several injection techniques (linear, threading, fanning, depot and/or cross-hatching). A depot or small bolus injection can be used in the areas of the upper zygoma or temples. Massage of the product is performed at intervals during injection. No overcorrection is required. Final outcomes with PLLA are delayed and require multiple sessions, spaced every 4 to 6 weeks apart, to allow adequate time for augmentation and avoid overcorrection. The principle should be one of serial application to achieve augmentation goals. Patients should be counseled on the length of the process and goals with each subsequent application. In addition it should be noted that areas treated with PLLA are likely to decrease in volume within the first 24 to 48 hours as the body reabsorb the sterile, bacteriostatic injectable water within the solution. Smooth massage will distribute the Sculptra evenly. Periodic massaging during all treatment sessions may help evenly distribute the product and reduce the risk for papule formation.

## Potential Complications

Overall, device-related adverse reactions are rare, and those that do occur do so as a result of incorrect reconstitution, poor injection technique, overcorrection, and deficient injection technique [25,26]. Thus, it is essential that the injecting physician follow the proper guidelines laid out in the product information provided with each vial of PLLA to avoid these adverse events. It is important enough to repeat that the injector not overcorrect as is sometimes done with other injectable fillers [25]. The results from PLLA are gradual and progressive and must be tracked over time. Failure to follow these techniques and guidelines may result in SPs, which form from improper dilution of PLLA and improper injection technique [26]. These injection-related papules may be prevented with proper dilution, a properly mixed suspension, proper injection depth, and vigorous massage. If papules or nodules form and the patient is distressed, it may be necessary to consider treatment of excision of papules. It should be noted that although these bumps can be palpable to the patients, they are often invisible and nonpathological. A bump resulting from a foreign body reaction will respond to a dilute triamcinolone injection. A bump resulting from clumping of PLLA may require subcision (breaking up) of nodule with an 18-gauge needle followed by injection of sterile water to dilute the PLLA and massage or surgical excision. Granulomas have been noted in the past as with all fillers. Late-onset granulomas may be surgical excision. Granulomas have been noted in the past as with all fillers. Late-onset granulomas may be treated with triamcinolone, fluorouracil, or methylprednisolone. Systemic therapy with low- dose prednisolone, doxycycline, or tetracycline has also been reported [27]. Additionally, injections into infected or inflamed skin are to be avoided. Patients who are allergic to any ingredients in PLLA should not be treated with the product [25].

A patient affected by facial lipoatrophy HIV-related treated with poly-l-lactic acid. First picture on the left is the pre-op; the one in the middle is the result after one filling sit, once

that the saline solution used to restore the poly-l-lactic acid is resorbed; on the right the result after six filling sessions.

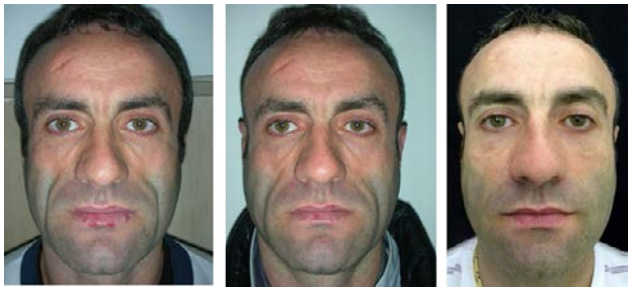

**Figure 5-7:** Final outcomes with PLLA are delayed and require multiple sessions, spaced every 4 to 6 weeks apart, to allow adequate time for augmentation and avoid overcorrection. The principle should be one of serial application to achieve augmentation goals. Patients should be counseled on the length of the process and goals with each subsequent application. In addition it should be noted that areas treated with PLLA are likely to decrease in volume within the first 24 to 48 hours as the body reabsorb the sterile, bacteriostatic injectable water within the solution.

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## Chapter 7

# Botulinum Toxin Type a Treatment in Facial Rejuvenation

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## Abstract

In this chapter we analyze the ever expanding potential uses of botulinum toxin in medical practice focusing on its cosmetic used in facial rejuvenation. We see how, from a single region and procedure for the treatment of the glabellar lines, the use of botulinum toxin has evolved into multiple areas, techniques, dosages and now new toxins in this ever expanding field. We focus on the use and dilutions of the two best-known botulinum toxin type A commercial products, making a distinction between their "label" and "off-label" uses. We consider that a thorough knowledge of the process of the facial aging and pertinent anatomy of the facial musculature is paramount to treat the patients successfully. We provide tips and hints on patient's management, from the selection through the assessment to the post-treatment care. We describe the clinical applications and preferred techniques used when injecting the mimetic facial and neck muscle with a detailed description for each clinical indication that maximize the treatment of the targeted muscles while minimizing potential complications. Finally we point out how the new concepts of aging and rejuvenation are opening new paths on the use of botulinum toxin together with other medical and surgical procedures in combined treatments.

## Introduction

Botulinum Toxin type A (BTX-A) has dramatically transformed the aesthetic care of the aging face since its initial FDA approval in 2002 for the temporary treatment of glabellar lines. BTX-A injection continues to be the single most common aesthetic procedure in the USA and Europe, although its use is accompanied by growth in the use of other modalities, including dermal fillers [1]. The clinical uses of BTX-A are extensive and in continuous evolution. The "ideal" candidates are men and women between 40 and 60 years of age whose skin wrinkles have been formed by habitual muscle contraction [2]. Cosmetic indications have extended to include the treatment of hyperfunctional facial lines in the forehead,

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periorbital, perioral and neck regions, as well as facial asymmetry and muscle spasm. All of these aforementioned uses are non-FDA approved ("off-label"), though legal indications of BTX-A when managed by licensed physicians. Botulinum toxin has also been employed to treat strabismus [3], cervical dystonia [4], hyperfuntional larynx [5], pain and headache [6], temporomandibular disorders [7], bruxism [8] and several other conditions [9]. The treatment with BTX-A belongs to the broad field of nonsurgical rejuvenation procedures who are directed at the texture and quality of the skin and volume deficiencies in the dermis and underlying soft tissues. The most important goal of BTX-A treatment in cosmetic medicine is to achieve a balance between dynamic rhytids caused by hyperactive muscles while maintaining natural facial animation. Different kinds of nonsurgical treatment of the facial aging are available and depend on the nature of the deformity (wrinkles, folds, furrows), on the skin layer in which the defect occurs or on the technique used to treat it (exfoliation, dermal and subcutaneous fillers, resurfacing, and chemodenervation). Optimal treatment often requires a multifaceted approach due to the many causes of wrinkles, various anatomic locations, individual patient preferences and the effects of aging; therefore the treatment should be individualized according to the causes and the patient's anatomy, goals and tolerance. Nonsurgical methods are often performed together and also in conjunction with surgical procedures to complement, enhance, or address a condition that cannot be corrected through surgery alone [10,11].

## Structure and Mechanism of Action

Botulinum Toxin (BTX) specifically and physiologically denervates the muscle targeting the release of acetylcholine. BTX is produced by the anaerobic bacterium Clostridium Botulinum. It is a gram-positive, spore forming obligate anaerobe that is found naturally in the soil. It is produced by fermentation of strain C. Botulinum Type A grown in a culture medium. In order to be used as a drug the toxin has to be isolated, purified and stabilized. There are seven serotypes of botulinum neurotoxins (A, B, C1, D, E, F, and G) produced by different strains of C. botulinum with serotype C2 being cytotoxic and not neurotoxic. The human nervous system is susceptible to five toxin serotypes (A, B, E, F, G) and unaffected by the rest. Although all toxins have different molecular targets, their action leads to the blockade of the cholinergic nerves. However, only the A and B toxins are available as drugs. All of the botulinum neurotoxins are synthesized as single-chain proteins of approximately 150-kDa that must be nicked or cleaved by proteases into di-chain molecules of approximately 100-kDa and 50-kDa subunits in order to be active [12]. Cleavage results in a di-chain molecule consisting of an approximately 100-kDa heavy chain and an approximately 50-kDa light chain, linked by a disulfide bond (Figure 1) [13]. Botulinum producing organisms may be classified as proteolytic or non-proteolytic, denoting the presence or absence of endogenous enzymes that cleave the 150-kDa single chain neurotoxin into the active di-chain neurotoxin [14]. Type A-producing strains are proteolytic and nearly all of the toxin recovered from these organisms (>95 per cent) exists in the di-chain form and this makes Botulinum Toxin type A the most powerful and long lasting of all the subtypes [15]. Type B-producing strains may be either proteolytic or non-proteolytic. Proteolytic type B strains have been found to cleave approximately 30 per cent of the single-chain proteins, although the percentage nicked in the commercial product based on the B serotype may be significantly higher [16]. Clostridial strains that synthesize toxin serotypes E and F are nonproteolytic and the toxin they produce must be exposed to exogenous proteases in order to exert its activity [17,18]. Botulinum neurotoxins are produced as part of a multimeric protein complex consisting of the neurotoxin and associated hemagglutinin and non-hemagglutinin proteins [14]. The number and identity of the associated proteins vary by serotype and organism. The associated proteins serve to stabilize and protect the neurotoxin molecule from degradation

[19,20]. Both A and B neurotoxins can be found in a 500-kD form but A can also be found in a 900-kD form, and this has been the size reported for the crystallized type A toxin used clinically (Figure 2) [21,22]. The toxin produces chemodenervation by preventing release of acetylcholine at the neuromuscular junction of the peripheral nervous system and at ganglionic nerve terminals of the autonomic nervous system within 6 to 36 hours of exposure to muscle with maximum effect up to 7 to 14 days [11]. Acetylcholine is a common neural transmitter and stimulates striated as well as smooth muscles and the secretion of glands such as sweat glands. In both A and B neurotoxins the heavy chain acts like a "Key in the Lock" and is responsible for selective binding of the toxin molecule to high affinity external receptors situated on the membrane of presynaptic cholinergic nerve terminals. The light chain acts inside the cell to prevent acetylcholine release. Within the cell, the light chain of type A cleaves SNAP 25, a 25-kD synaptic cell-associated protein, while the light chain of type B cleaves Vesicle-Associated Membrane Protein (VAMP). This chain of events brings to the flaccid paralysis of the targeted muscle or the functional block of the glandular activity [23].

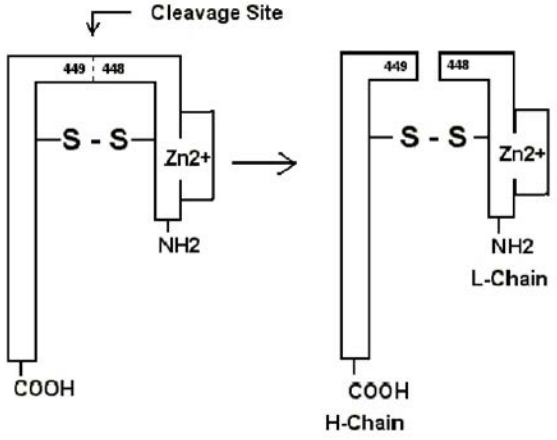


**Figure 1**: Schematic structure of the single-chain neurotoxin and cleavage site and its transformation into the active di-chain neurotoxin.

Botulinum Toxin blocks neuromuscular transmission through a three step process. First, the toxin binds to presynaptic cholinergic motor nerve terminals. Next, the toxin is internalized into the nerve terminal by endocytosis, where it eventually enters the cytoplasm. Finally, it inhibits acetylcholine release by cleaving a cytoplasmatic protein (Figure 3).

At therapeutic doses the toxin induces paralysis limited to the injected muscle; however, the toxin has the potential to cause paralysis or weakness of adjacent muscles by diffusion and spread. Diffusion results from toxin moving down its concentration gradient, which is affected by local receptor concentration whereas spread depends on the solution volume and injection technique (physically pushing the toxin from the area of injection). Depending on the strength of the muscles treated and the dosages used, the duration of the effect varies from a couple of months to several months. The action of the drug slowly decreases over time as the affected axons sprout new nerve terminals which continually restore the impaired transmission. During this phase the damaged synapse itself will regenerate its function so that the sprouts regress as the clinical effects of the drug subside [24]. The muscular function gradually returns after 3 months and axonal sprouting and reorientation of muscle fibers prevent permanent paralysis of muscles that are treated repeatedly [11,25].

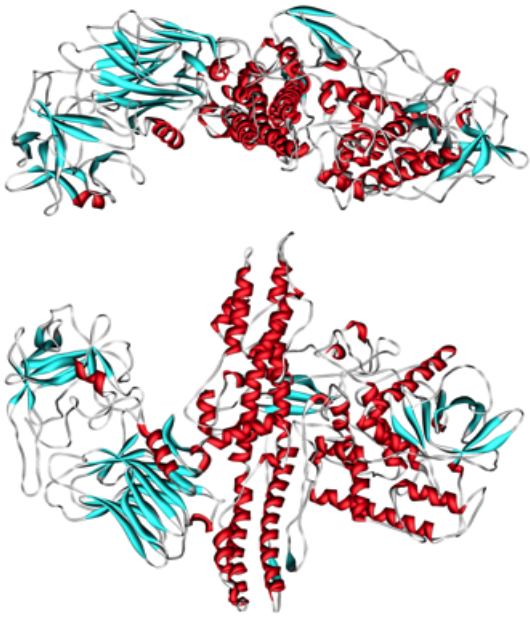

**Figure 2**: Molecular structure of botulinum neurotoxin 3D.

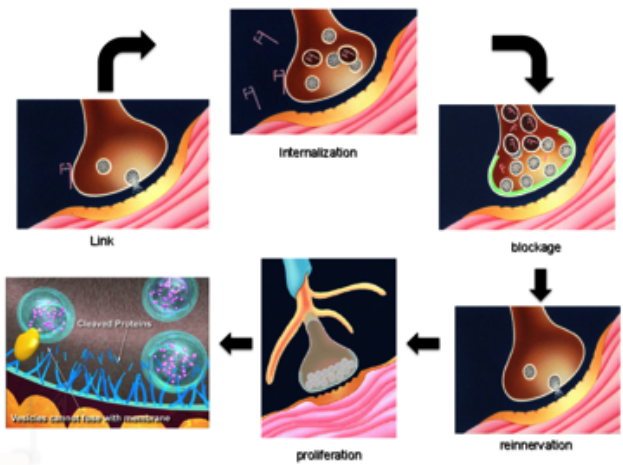


**Figure 3**: Mechanism of action.

## Toxicity

Botulinum toxin is one of the most potent toxins known. It is estimated that in a 70Kg adult, the lethal dose of crystalline botulinum toxin type A would be approximately 0.09 to 0.15 mg by the intravenous or intramuscular route, 0.7 to 0.9 mg by inhalation and 70 mg if ingested orally. The toxin does not penetrate intact skin, and person to person transmission does not occur [11]. The lethal dose of Botox/Vistabex (Onabotulinumtoxin A) is measured in units, with 1 unit being the lethal dose of toxin causing death in 50% of a group of 18 to 20gm female Swiss Webster mice within 3 days of intraperitoneal injection. The median

lethal dose has been estimated to be 2700 (2500 to 3000) units in a 70 kg human, based on the median lethal dose of approximately 40 units/kg in primates [11]. Note that units of Dysport/Azzalure (Abobotulinumtoxin A) are expressed in Speywood Units (S.U.).

## Different Products

The three most widely available BTX products approved for cosmetic indications are Onabotulinum Toxin A (OnT-A); Abobotulinum Toxin A (AbT-A) and Incobotulinum Toxin A (InT-A). Botox is the original OnT-A product, approved in 2002 by the FDA, it is produced by Allergan Inc. and it is marketed for cosmetic use in the US as BOTOX Cosmetic®, in Italy as Vistabex® and in the rest of Europe as Vistabel® [26]. Dysport® (Medicis Aesthetics Inc., Scottsdale, AZ, USA), approved in 2009 for cosmetic use [27] is currently marketed in Europe under the commercial name of Azzalure® (Galderma, Germany). More recently, another BTX-A formulation, under the non-proprietary name of incobotulinum toxin A (Xeomin® or Bocouture®; Merz Pharmaceuticals GmbH, Frankfurt, Germany) has received approvals for cosmetic use in many countries including Italy (Figure 4) [28]. In the Asian countries we can also find the recently released Chinese BTX-A (Prosigne®, Lanzhou Biological Products Institute, China) and Neuronox® (Medytox Inc., Ochang Science Complex, Chungcheongbukdo, Korea). Worth mentioning is the recently developed BTX-A toxin named PurTox® (Mentor Corporation, Santa Barbara, CA) which will be ready to hit the market real soon. Among these products, BOTOX is the most commonly used worldwide for all indications, followed by Dysport. NeuroBloc®, also marketed as Myobloc® (Solstice Neurosciences Inc.) is the only commercial available type B BTX. Although there is some data on its efficacy in aesthetic indications, it is not often used for these indications [29,30]. Cervical dystonia is currently its sole approved indication [31]. The authors' personal experience is limited to Vistabex® (or Botox Cosmetic®) and Azzalure® (Dysport®), which will then be the subject to this chapter. Both Azzalure®/Dysport® and Vistabex®/Botox® are supplied in a sterile vial, fitted with rubber stopper and sealed with an aluminum cap, containing botulinum toxin type A in the form of a sterile, lyophilized powder without preservatives in vacuum packed. Each vial of Dysport® contains 300 units of botulinum type A complex, 125 ug of human serum albumin, 2, 5 mg of lactose, and trace amounts of cow's milk protein. A 500-unit vial of Dysport® is also available for cervical dystonia. Azzalure®, commercial trademark in Europe, is distributed in a 125-unit vial. Botox Cosmetic® (Vistabex®/Vistabel®) is supplied in a vial with 100 units of dried neurotoxin complex, 0.5 mg of human albumin and 0.9 mg of sodium chloride. A 50-unit vial of Botox Cosmetic® (Vistabex®/Vistabel®) is also available.


**Figure 4:** Most common used commercial products of Botulinum Toxin Type A.

It is important to note that 100 units of Botox cosmetic® is not equivalent to 100 units of Dysport®. Before use vials should be stored in a refrigerator at a temperature of 2-8°C and could be stored for up to 24 months. In order to be injected, the reconstitution is performed

with sterile 0.9% unpreserved normal saline [32] although studies have demonstrated that preserved saline provides increased patient comfort without decreasing efficacy [33]. If the reconstituted product isn't injected immediately, it must be stored in the refrigerator for no longer than 24 hours, although some studies suggest that the activity can be maintained for up to 6 weeks after reconstitution [34]. Most practitioners discard unused reconstituted toxin after 1-7 days. Before injecting the rubber stopper can be removed from the vial before mixing to prevent foaming and the saline solution is introduced by means of a 1ml Luer-Lok syringe with a 22- or 25-gauge needle. The same needle is used to withdraw the reconstituted solution and is then replaced with a 30- or 32-gauge needle, which is used for injection.

Although there are no special handling precautions when using Botox, it is important to note that alcohol could neutralize the toxin. Therefore, if the practitioners use alcohol to prepare the skin, it should be allowed to dry before injection.

## Dilution Considerations

The recommended dilution for Botox Cosmetic®/Vistabex® ranges from 1 to 4 ml per 100 unit vials (0.5-2 ml per 50 unit vial). The manufacturer's recommendations and initial FDA approval for the treatment of glabellar lines were based on 2.5 ml (0.1 ml = 4 units) of unpreserved normal saline solution per 100 units [35]. The maximum total recommended dose is 300 to 400 units at any one session and not more than 400 units over a 3-month period [11]. The recommended dilution for the 300 unit vial of Dysport® is 2.5 ml of 0.9% sodium chloride to yield a solution equivalent to 10 units per 0.08 ml. It can also be reconstituted with 1.5 ml of sodium chloride for a solution of 10 units per 0.05 ml. Each 500-unit vial is reconstituted with 5 ml of saline to yield a solution of 10 units per 0.1 ml. The recommended dilution for the 125-unit vial of Azzalure® is 0.63 ml of normal saline to prepare a solution of 10 units per 0.05 ml [26]. The maximum total recommended dose is 1000 units at any one session. As aforementioned we have to be aware of the differences in dosing between Botox Cosmetic®/Vistabex® and Dysport®/Azzalure®, since the units are not interchangeable. Azzalure®/Dysport® is less active on a unit-per-unit comparison with Botox Cosmetic®/Vistabex®, which means that more units of Azzalure®/Dysport® are required to achieve similar clinical effects. The FDA mandated in 2009 that all BTX-A product labels clarify that the potency units for each product are specific to each preparation, however, in common practice many providers have used a dose (unit) equivalent ratio of Botox® and Dysport® of 1:2.5 or 1:3 suggested in the literature. Note that the use of this conversion ratio is most appropriate when considering the safety profile of the product, not its efficacy [36-39]. For what concern Incobotulinum toxin A (Xeomin®/Bocouture®) the recommended dilution with unpreserved saline is 1.25 ml per 50 units, giving a final concentration of toxin of 40 units/ml [40]. In terms of potency, Xeomin®/Bocouture® appear to exhibit a 1:1 dose ratio when comparing with Botox [41]. The reconstitution, dilution, and storage are matters of physician preference and the providers will develop a familiarity with the efficacy of each formulation of BTX-A through experience (Table 1).

| Type and Concentration of Botulinum Toxin | |
|---|---|
| **Type of Botulinum Toxin** | **Concentration (units/ml)** |
| Dysport® 300 - unit vial | |
| 1 ml | 30/0.1 |
| 1.5 ml | 20/0.1 |
| 2.5 ml | 12/0.1 |
| 3 ml | 10/0.1 |

| Azzalure® 125 - unit vial | |
|---|---|
| 0.63 ml | 10/00.5 |
| Botox Cosmetic® Vistabex® , Vistabel® 100 -unit vial | |
| 2 ml | 5/0.1 |
| 2.5 ml | 4/0.1 |
| 4 ml | 2.5/0.1 |
| Botox Cosmetic® Vistabex® , Vistabel® 50 - unit vial | |
| 1 ml | 5/0.1 |
| 2 ml | 2.5/0.1 |

**Table 1:** Recommended dilutions for Botox Cosmetic®/Vistabex® and Azzalure®/Dysport® [11].

After intramuscular injection, botulinum may spread or diffuse. "Spread" occurs immediately after the injection itself, which is related to technique, volume of injection, and needle size. "Diffusion" occurs over several days as the toxin passively moves away from the injection site [42]. Generally Azzalure®/Dysport® has a larger area of action, and there has been ongoing debate regarding the difference in onset between Botox Cosmetic®/Vistabex® and Azzalure®/Dysport® [43]. Based on the concept of diffusion and spread it has to be kept in mind that the mimic muscles of the face are in a very intimate relationship in between themselves, therefore, to achieve the most accurate effect on the targeted muscle we should use highly concentrated doses of the drug, injected by means of very small volumes of solution [44]. In general large dilutions with lower concentrations of toxin require larger volumes of injections to achieve the desired result, which can increase the potential for spread of the toxin to unwanted surrounding areas. The general trends currently agree on the use of low volumes on high concentrations of toxin [45].

## Infiltration Technique

A 30-gauge 1-inch needle is used to perform the injections. Topical anesthesia with ice or other agents may be beneficial to decrease pain associated with injections but is not necessary. In order to estimate the expected benefit from botulinum toxin A injection, a glabellar "spread test" may be performed prior to injecting by spreading the glabellar wrinkles apart with the thumb and index fingers. Patients with sebaceous skin and deep dermal scarring that are not improved with manual spreading usually respond poorly to BTX-A injection. With the exception of the perioral and periocular areas, injections should be made into the muscle belly perpendicular to the skin. The needle is advanced to the periosteum and then withdrawn slightly to place the needle in the muscle. It is useful to use facial animation to mark the areas that require treatment. Injections should be made with the patient reclined to 45°C even though some authors prefer the patient to sit in the upright position or lay down completely. When injecting, the skin should be slightly stretched to assist in identifying superficial vessels that can be avoided to decrease the risk for ecchymosis. If a bruise starts to develop, the practitioner should hold 5-10 minutes of pressure to avoid a hematoma, which could lead to migration of the toxin. The injection should be performed slowly in order to minimize discomfort. Patient should be told not to massage the area as it may cause diffusion of the drug and result in weakness of unintended muscles. Patients should also be advised to contract the treated areas as it may increase local uptake of the toxin [11]. It is preferable to start treatment with the lowest dose so to test patient responsiveness and, if required, to increase botulinum units in succeeding sessions.

## Microinjection Technique

The microinjection technique is used to administer low doses of botulinum toxin very superficially. BTX-A applied by microinjection technique in the crow's feet area will decrease the risk of an involuntary co-treatment of the m. zygomaticus major. The microinjection technique follows an intradermal approach; small amounts of toxin (less than 0.025 ml) are injected approximately 1 cm apart, very superficially, in a technique comparable to the intradermal skin test.

## Patient Selection

Experience has changed the way BTX-A is now used. Patient's feedback after the injections and the analyses of results has led to the understanding that muscular inhibition does not necessarily promote a cosmetic upgrade. The feared "frozen look" belongs to the past and both patients and injectors understand that a natural look is desired. Treatment with BTX-A injection should be individualized. The duration of effect changes from patient to patient because every individual is different and so is muscular behavior. Some of the patients are symmetrical while others are quite asymmetrical. Other patients have single muscle insertions while others may have multiple muscle insertions, which may also vary the choice of treatment. Certain patient characteristics and anatomic features help to define good, or conversely, less acceptable candidates for botulinum toxin injection. De Maio et al., classify the patients into three groups before treatment, based on their muscle tonus; kinetic, hyperkinetic and hypertonic. The Kinetic patients are the easiest to treat, especially for the beginner, and the duration effect is the longest among the groups. The hyperkinetic patients are victims of excessive muscular contraction and they usually return for treatment twice or three times a year depending on when the effect starts to fade, being the most common group for BTX treatment. The last ones, the hypertonic patients represent the negative result of lack of control of the hyperkinetic ones. They are the group that particularly needs treatment and usually get frustrated with. The result in these patients is the shortest of all groups and they should be told immediately about the limitations of treatment with BTX-A alone and should be treated with fillers or other surgical methods [46,47].

## Patient Pre-Treatment Assessment

The practitioner has to take record of the medical history of the patient including prior treatments with botulinum toxin, topical agents or injectable fillers. The facial features have to be evaluated both at rest and in maximal facial animation to best understand the anatomic extent and relative strength of the target muscle. This information will dictate modifications in the dose required for the desired effect [9]. The patient is instructed to accentuate the specific facial lines to be treated by frowning, squinting and elevating the brow. Clinician should set realistic expectations and discuss if off-label use is planned. The patient should be fully aware of the cause of his or her condition and the potential role of botulinum toxin in improving it; the practitioner should explain that the toxin's mechanism of action is to address hyperkinetic muscles of facial expression, causing them to relax and therefore releasing the overlying wrinkle rather than filling it in or sanding it down and that the effect of the toxin may not manifest for 24-72 hours after injection, with optimal result seen at 2 weeks. The patient should be informed that the results typically last 2-3 months, even though some authors have reported results lasting 6 months or more [34,48-52] and also that an assessment and possible retreatment should be done 14 days post-injection when the maximum effect of the toxin has been reached. Planning for concurrent dermal filler or subsequent surgical treatment can be discussed. Most important is to evaluate the patient for pre-existing ptosis in order to discuss with him/her the actual risk/benefit of the treatment. Patients are instructed to avoid using aspirin products, vitamin E, nonsteroidal anti-inflammatory agents and dietary supplements that predispose

them to bleeding or coagulation problems, for 10 to 14 days before treatment to minimize ecchymosis [53,54]. Pretreatment photography is highly recommended to document any pre-existing asymmetry, to assess efficacy and to guide pre and post-injection treatment plans. As with any aesthetic procedure photodocumentation is fundamental to help resolve any issues raised by the patient following treatment. An informed consent is required, with detailed mention of possible complications. In general the main side effects that a patient may encounter include: pain at the injection site, bruising and unexpected weakness of muscle groups (for example eyelid ptosis) [55,56].

### Contraindications to BTX treatment

To avoid adverse events certain contraindications have to be ruled out prior to the treatment with botulinum toxin. Patients with hypersensitivity to the ingredients (Albumin, sodium chloride, botulinum toxin); neuromuscular disease (myasthenia gravis, Easton-Lambert syndrome, motor neuron disease); patients treated with BTX concurrent with other drugs that interfere with neuromuscular transmission such as antibiotics (aminoglycosides, lincosamides, polymixins), penicillamine, quinine, calcium channel blockers, neuromuscular blocking agents (atracurium, succinylcholine), anticholinesterases, magnesium sulfate and quinidine, all of which may increase the paralytic effect of the toxin; pregnant or lactating women; patients receiving anticoagulation therapy/aspirin; patient with inappropriate anatomy (skin laxity, photodamage) and finally patient with poor psychological adjustment or unrealistic expectations (dysmorphism) [11,57-59].

### Markings

Markings are usually not necessary because the patient is asked to repeatedly contract the muscle to identify sites for injection. If the patient is having BTX-A injections intraoperatively, markings are made over the body of the muscle, not over the deepest dermal rhytid.

## Anatomy of the Facial Musculature

The use of botulinum toxin for rhytids or to reshape or reposition structures requires an in-depth understanding of the function and the location of the muscle of the face, their interactions (agonist versus antagonist) and the unique anatomic features of each region of the face (Figure 5).

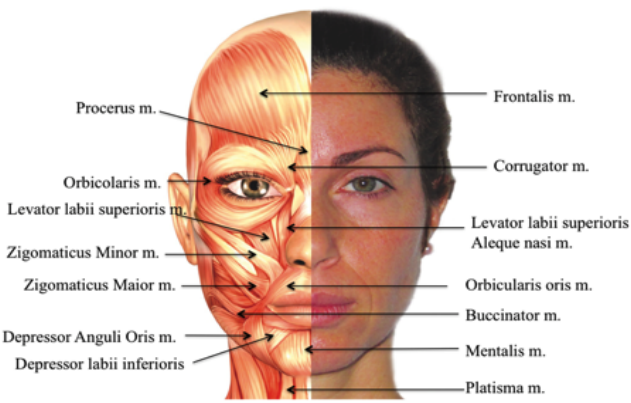


**Figure 5**: Pertinent anatomy of the facial musculature.

## Anatomy of the forehead

The venter frontalis of the m.occipitofrontalis is part of the m. epicranius. It derives from the skin of the eyebrows and glabella and intervenes with the fibers of the m. orbicularis oculi. It follows upwards where it inserts into the galea aponeurotica, the extended tendon of the m. epicranius. This muscle leads, when contracted, to the horizontal lines of the forehead. It raises the eyebrow and the upper lid and by this makes the eye look open and much bigger [60,61].

## Anatomy of the eye region

The *m. orbicularis oculi* is innervated by the temporal and zygomatic branches of the facial nerve. The *m. orbicularis* arises from the nasal portion of the frontal bone, the frontal process of the maxilla and the medial palpebral ligament. It is composed of three portions: orbital, palpebral and lacrimal. The orbital portion forms the majority of the muscle bulk. Fibers are arranged in an elliptical pattern and present no interruption laterally. The superior orbital portion of the orbicularis oculi runs more superficially than the m. corrugators and blends medially into the frontalis. Laterally, the muscle extends over the temporal fascia. Inferiorly, it continues and covers the upper portion of the m. masseter. More medially, at the inferior orbital margin, its extension covers the elevators of the upper lip. The palpebral portion originates from the medial palpebral ligament and adjacent bone. It is subdivided into preseptal and pretarsal portions. The pretarsal fibers spread across the eyelids, the preseptal fibers course in front of the orbital septum and both fiber interdigitate laterally with the lateral palpebral raphe. The ciliary bundle is a small group of fine fibers lying at the palpebral margin. The lacrimal portion has both superficial and deep heads that arise from the medial palpebral ligament and the posterior lacrimal crest. The fibers extend laterally to attach to the tarsi and to the lateral palpebral raphe [60,61].

## Anatomy of the glabellar region

Glabellar lines are created by three muscles: the *m. depressor supercilii*, *m. corrugators* and the *m. procerus*. The *m. depressor supercilii* is the medial part of the orbicularis oculi pars orbitalis. It derives from the ligament palpebrale mediale and inserts in a fan shape cranially in the dermis of the medial part of the eyebrow. Contracting the *m. depressor supercilii* will draw the eyebrows down and will give this person a menacing expression. The *m. corrugator's supercilii*, also seen as an independent deeper part of the orbicularis oculi pars orbitalis derives from the medial orbital ring and gradually proceeds laterally to where the muscle inserts above the middle of the eyebrow in the dermis. Contracting the m. corrugators supercilii leads to vertical lines between the eyebrows. The *m. procerus* originates from the bridge of the nose and inserts into the skin of the glabella. Its fibers are interwoven with the frontalis ventral fibers of the m. occipitofrontalis. Contracting the *m. procerus* will induce a horizontal line between the eyebrows [60-63].

## Anatomy of the upper third of the face

The facial upper third extends from the hairline to the top of the eyebrows. In men with receding hairlines, the upper part of the forehead equals the superior aspect of the frontalis muscle. Its normal resting tension is responsible for the normal position of the eyebrows. The galea aponeurotica covers the skull, just beneath the fat. The *m. frontalis* is the anterior part of the occipitofrontalis muscle. In front of the coronal suture, the aponeurosis gives origin to and is partly hidden by the frontalis bellies, which descend without any bone attachment to blend with the m. orbicularis oculi. The medial fibers of the *m. frontalis* blend with the m. procerus fibers and become contiguous at the nasal level. The *m. frontalis* has

two halves and in the superior aspect of the midline forehead there is no muscle, but a fascial band. The usual action of the *m. frontalis* is to raise the eyebrows in the expression of surprise and even higher with freight, and to furrow the forehead with transverse line with thought. The eyebrows have one elevator and three opponents as depressors: the m. corrugators, the m. procerus and the m. orbicularis oculi [60,61].

**Anatomy of the Nose – "Bunny lines"**

The skin is thinner and more mobile in the upper two thirds of the nose, and it is thicker and more adherent in the lower third. The nose contains three main muscles: the m. procerus, the *m. nasalis* and the *m. depressor septi nasi.* The *m. procerus* draws the medial part of the eyebrow down. The m. depressor speti nasi drops the tip of the nose when contracted and the *m. nasalis* is the most important one for promoting the bunny lines. Although the *m. levator labii superioris alaeque nasi* is not an intrinsic nasal muscle, it may contribute to the bunny lines due to its medial fibers. The *m. nasalis* originates in the transition from the nasal bone with the maxilla and inserts into the aponeurosis of the nasal dorsum. It looks like an upside-down horseshoe, with the curved part formed by transverse fibers on the nasal dorsum. Its action is to narrow the nostrils. The transverse fibers of the *m. nasalis* lead, when contracted, to the lateral nasal lines (bunny lines) and to additional lines in the internal infra-ocular region. The two lower parts of the *m. nasalis* run vertically down the sides of the nose and their action is to open the nostrils. The *m. depressor septi nasi* is the most important muscle that acts on the position of the nose tip. Its origin is at the base of the nasal septum and it blends with the fibers of the orbicularis oris. Its fibers are longitudinal and, with contraction, it shortens the upper lip and can decrease tip projection on animation [60,61].

**Anatomy of the nasiolabial fold**

The nasolabial fold extends from the upper lateral part of the nasal flare down to the oral commissure. It can vary from individual to individual: be complete absent or flat or even very deep with skin excess and premaxillary deficiency. It can stop laterally to the oral commissure o go downward to the chin area. Nasolabial fold can result from more than one cause. It can result from the loss of skin thickness over the sulcus; from the presence of redundant skin drooping over the sulcus; from excessive fat deposits laterally to the sulcus; from ptosis and laxity over the malar fat pad and from muscular hyperactivity. The muscles at the nasolabial level, from medially to laterally, are the *m. levator labii superioris alaeque nasi*, m. levator labii superioris, *m. zygomaticus* minor, *m. zygomaticus* major and at a deeper level, the *m. anguli oris*. It is important to underline that the zygomaticus major has little or no effect on the nasolabial fold. The *m. levator labii superioris* is the main elevator of the upper lip and functions to create and move the middle portion of the nasolabial fold. It originates from the lower margin of the orbit, above the infraorbital foramen and below the orbicularis oculi. It continues downward between the levator *labii superioris alaeque nasi* and *zygomaticus* minor and inserts into the central and lateral aspects of the upper lip. It elevates and everts the upper lip. The *m. levator labii superioris alaeque nasi* originates from the frontal process of the maxilla and descends and divides itself into two muscle bundles: the most medial smaller fibers insert into the nasal cartilage and the skin of the nose and a larger and more lateral bundle continues downward and inserts into the upper lip, merging its fibers with the *m. levator labii superioris* and with the *m. orbicularis oris*. The *m. levator labii superioris alaeque nasi* creates the medial most upper portion of the nasolabial fold. Its medial nasal muscle bundle dilates the nostril and displaces the sulcus laterally, elevating the nasolabial fold. The labial muscle bundles evert and elevate the upper lip [60,61].

## Anatomy of the oral region

The orbicularis oris is a sphincter around the mouth. It is a bilateral circumferential muscle that closes and puckers the mouth and forms a purse string. It anchors to the nasal septum and the maxilla above and to the medial part of the mandible below. The deeper layer of the orbicularis oris are the fibers of the buccinators and are reinforced by the incisive bundles. From the skin, short oblique fibers traverse the thickness of the lip in the direction of the mucosa. The more superficial layer is formed by the insertion of seven small muscles: five elevators and two depressors. At the corner of the mouth there is an area denominated modiolus, it is where the muscles that elevate and depress the lip interdigitate. The elevators consist of the *m. zygomaticus* major and minor, *m. levator labii inferioris*, *m. levator labii superioris alaeque nasi* and *m. levator anguli oris*. The zygomaticus major muscle originates from the zygoma (anterior to the zygomaticotemporal suture) and runs inferiorly and medially to the angle of the mouth and contributes to the modiolus. The zygomatic minor muscle arises from the malar bone (behind the maxillary suture) and passes downward and inward and in continuity with the *m. orbicularis oris* at the outer margin of the *m. levator labii superioris*. The action of the *m. zygomaticus* major is to elevate the corner of the mouth and it has little or no effect on the nasolabial fold. It is both the *m. levator labii superioris* and the *m. levator labii superioris alaeque nasi* that create and move the middle and medial most portions on the nasolabial fold, respectively. The main elevator of the lip is the *m. levator labii superioris* and it arises from the lower margin of the orbit just above the infraorbital foramen and its fibers insert into the midportion of the nasolabial fold. The *m. levator labii superioris alaeque nasi* arises from the frontal process of the maxilla and inserts on the alar cartilage and medial upper lip. It dilates the nares and everts and elevates the medial upper lip. It deepens the medial upper nasolabial fold. The depressors consist of the *m. depressor anguli oris* and the *m. mentalis*. The *m. depressor anguli oris* belongs to the most superficial part of the perioral muscles of the lower lip and chin. It is a triangular muscle that derives from the base of the mandible and continues laterally and cranially. It inserts in the fibers of the corner of the mouth where it interweaves with the elevators of the mouth, the *m. levator anguli oris* and the m. zygomaticus major. The *m. depressor anguli oris*, together with the fibers from the platysma, drags the corner of the mouth down. This movement will induce a visible crease ("Marionette Lines") that descends from the corner of the mouth and gives the total face a dissatisfied and sullen expression. The *m. mentalis* belongs to the muscles of the perpendicular system of the perioral area and is the most medial and deepest muscle of this area. It derives from the lower incisors and inserts transversally in the dermis of the chin. The muscles from both sides crisscross each other. While contracted, the chin may show a "cobblestone" patter. Moreover, the mentolabial crease might be increased while showing the lower lip forward [60,61].

## Anatomy of the lip

The lips comprise the red part of the mouth as well as the skin adjacent to it. Both parts must be considered as an anatomic unit that reaches from the nose to the chin. Perfect lip structure in the mucosa and skin consist of a "V-shaped" Cupid's bow, a pronounced vermillion and medial tubercle as well as ascendant lines in the oral commissures. The ratio between the upper and lower lips, at golden proportions, is 1:1.618. A very important topographic landmark is the philtrum. The midpoint of the upper cutaneous lip is highlighted by the two vertically oriented ridges of the philtrum. The Cupid's bow is the concavity at the base of the philtrum. The skin of the upper lip is very thin and lacks subcutaneous fat. The lack of additional support of this area together with extensive muscular movement of the main muscles may lead to pronounced wrinkles. The *m. orbicularis oris* is the major muscle of the lips. It has circumferential fibers that are responsible for the sphincter function of the mouth [60,61].

### Anatomy of the neck region

The platysma is the largest mimic muscle. It originates at the border of the lower jaw, covering the chin up to the angulus mandibulae. The lateral fibers of this muscle extend over the angulus mandibulae in the area of the lower cheek and also radiate towards the corner of the mouth, where the interwine with the other muscles of the modiolus. The caudal part of the platysma runs as a broad thin sheet of muscles towards the clavicle and inserts approximately around the second rib at the fascia pectoralis. The platysma does not usually cover the medial area where the cartilage of the larynx can be found. The platysma covers the superficial fascia of the neck and is closely connected to the skin. It draws the lower jaw and the corners of the mouth down, expands the skin of the neck and extends the skin in vertical lines. In the area of the upper thorax, contraction of the platysma might cause diagonal wrinkles. When treating the platysma, the practitioner has to pay attention to the close relationship to the group of supra and infrahyoid muscles and to the outer larynx muscles. Apart from the diagonal *m. sternocleidomastoideus*, only the fascia of the neck will separate the platysma from the muscles of the larynx [60,61].

## Treatment of Anatomic Areas

The first cosmetic indication for botulinum toxin A was the treatment of glabellar lines for which Botox® and Dysport® received the U.S. FDA approval in 2002 and 2009 respectively. Both have been approved for "the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators and/or procerus muscle activity in adults younger than 65 years [27,64]. Xeomin®/Bocouture® recently received cosmetic approval for the treatment of glabellar lines in Germany, UK, France, Italy and Spain [28]. "Off-label" clinical indications have expanded to include hyperfunctional facial lines on the bridge of the nose, forehead, crow's feet, around the mouth, over the chin and bands in the neck. Additionally, non-cosmetic indications have developed for weakening mimetic facial muscles for disorders such as hemifacial spasm and facial dyskinesis. Further indications have been developed in the field of chronic pain management, which includes Temporomandibular Disorder (TMD) and headache [65,66]. Regarding the doses of toxin used for cosmetic purposes, it was concluded by a consensus committee that the dose of BTX-A should be adjusted in different anatomic areas depending mostly on muscle mass (contracted vs resting) and the desired degree and duration of effect [67]. Facial proportions may be an important consideration, for example, when injecting the frontalis to treat forehead lines. Other factors exist and may be interrelated; for example, wrinkle severity increases with age and men usually have larger muscles than women. Observing muscle action is the most important method for locating injection points in almost every anatomic area, followed by anatomic landmarks.

## FDA Approved Uses

### Glabellar complex/Vertical frown lines

Glabellar lines form as the result of frowning and may also persist in repose as approximately vertical, static lines between the eyebrows. This area may be treated by the "novice" injector, although a basic degree of training is needed before injecting in any area [67]. Medial brow depressors that form horizontal (procerus and depressor supercilii muscle) and vertical (corrugator's supercilii muscle) lines in the glabellar area are targeted. The aim of the treatment is to reduce the vertical as well as the horizontal lines of the glabella. Injections points for the glabella are best determined by observing muscle contraction, although palpation of the muscles and making references to superficial landmarks sometimes can be useful, as can bony landmarks and anatomic diagrams.

The most commonly used dose according to the literature is 20U of onabotuilinumtoxinA (Botox®/Vistabel®/Vistabex®) [68,69] and 50U of abobotulinumtoxinA (Dysport®/Azzalure®) [70-74] divided between five injection sites. This dose does not have to be divided equally among injection sites. These dosages are mainly referred to women patients but it has to be kept in mind that, on average, men need higher dose of botulinum toxin A than women to receive equivalent efficacy due to a larger mass being treated [9,75]. Injections should be made intramuscularly and perpendicular to the skin surface. Care should be used to avoid injecting superior to the target muscles, which can cause brow ptosis by weakening the frontalis [67]. In most patients, the first injection point is used to treat the *m. procerus* in the middle of an imaginary cross between the contralateral eyebrows and the medial corner of the eyelid. This area is massaged horizontally with the thumb, which safely distributes some toxin into the depressor supracilii [76]. The two most important points for treating the glabella are the injection points in the corrugator's muscles which are located 0.5-1cm above the medial orbital rim in extension of the exit of the *n. supraorbitalis* (the medial canthus can be used as a marker). After injecting in this location the needle is partially withdrawn but the tip kept beneath the skin, then repositioned until it angles superiorly and the tip advanced until it is approximately 1cm above the previous injection site and continue with the injection (Figure 6). A useful tip is to place the non-dominant index finger on the undersurface of the medial brow while injecting as an aid to avoid excessively deep insertion of the needle through the orbital septum and subsequent weakening of the levator palpebri muscle [9]. This "two hands" technique is also useful in identifying the bulk of the targeted muscle group that requires treatment. Injections should be no placed any further lateral than the midpupillary line to avoid loss of facial expressivity from weakening the lateral frontalis muscle and thus changing brow contour.

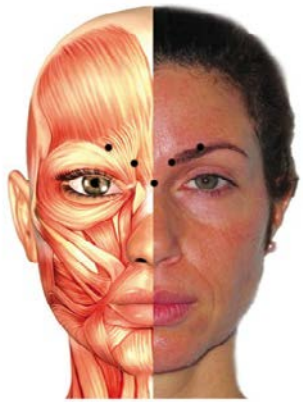

**Figure 6:** Injection points for glabellar treatment.

**Complications:** Injecting within 1cm of the bony margin of the orbit or near the supraorbital notch can cause eyelid ptosis by weakening the *m. levator palpebrae superioris* and this is certainly the effect least wanted [45]. Some authors have suggested that low-volume; high-concentration injection is one technique that can be used to minimize diffusion of the toxin to undesired muscles [57]. Ptosis can occur as early as 48 hours or as late as 7 to 10 days post-treatment. The degree of ptosis worsens throughout the day as the muscle fatigues. Proper injection technique is the best means to avoiding blepharoptosis. Pharmacological improvement can be accomplished with topical alpha-adrenergic agonists. Muller's muscle is stimulated with apraclonidine or phenylephrine eye drops administered several times per day [77-80]. Keep in mind that eyelid ptosis is temporary and usually subsides after a few weeks.

## "Off-Label" Uses

### Frontalis/Horizontal forehead lines

Forehead rhytids develop from hyperfunctional habitual activity of the frontalis muscle. One of the most undesired effects of over treating this muscle is the brow ptosis which is one of the major signs of aging. The medial fibers of the frontalis muscle are generally stronger than the attenuated lateral fibers and form deeper rhytids. Injecting only the medial frontalis muscle can yield a canted brow contour with a scowled expression. The horizontal rhytids are marked when the frontalis muscle is in maximal contraction. The number of injections varies from four to ten, depending on the severity of the rhytids with a dose range of 10 to 15U of onabotulinumtoxinA and 20 to 30U of abobotulinumtoxinA divided among all sites [9]. Injections are done perpendicular into the muscle 2cm above the brow and should be distributed in the middle of the forehead area. The more lateral points of injection will determine the degree of movement of the eyebrow; if the lateral injection point is placed in the midpupillary line, the lateral parts of the frontalis muscle will lift the lateral parts of the eyebrows upward which is preferable in female patients, whereas in male patients the lateral injection point should be placed in a line with the lateral corner of the eye (Figure 7) [81]. Complete immobilization of the forehead is often not desired, even if some lines remain, because it can prevent normal facial expression. The goal should be to weaken the muscle only [67]. Often the forehead is treated together with the glabella. When treated at the same time, the total dose might be reduced to avoid a frozen expression.

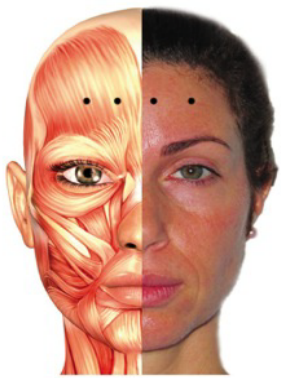

**Figure 7:** Injections points for forehead treatment.

**Complications:** Brow ptosis is the most common and unwanted adverse event. It may result from injecting the frontalis muscle within 1cm of the supraorbital rim, not simultaneously weakening the brow depressors, and from excessive delivery of toxin to the frontalis muscle, particularly in the elderly patient with undiagnosed senile brow ptosis [9]. This "caveman droop" is difficult to fully correct because the frontalis is the only muscle that can elevate the brows. For this reason it should be avoided to treat the lower part of the forehead [67]. If the frontalis muscle is not weakened at the same time as the glabella, excessive brow elevation can occur; especially in hypertonic patients the lateral movement of the frontalis muscle will produce more visible wrinkles or make the existing wrinkles more visible. This effect, variously called "Spock", "Joker" or "Mephisto" eyebrow, can be corrected with an injection of approximately 2U of onabotulinumtoxinA or 5U of abobotulinumtoxinA into the frontalis muscle above the point of maximum contraction [78].

## Brow lift

The aging process causes gradual descent of the forehead and brow, especially its lateral third. This makes the individual look tired and aged leading to a negative appearance. Eyebrow mal-positioning may cause upper eyelid fullness that may be targeted insufficiently by blepharoplasty alone. Eyebrow asymmetry is very common in middle-aged women and this makes eyebrow elevation a very important part of the world of cosmetic procedures. Eyebrow position differs between men and women. In women, the eyebrow should be positioned above the supraorbital rim, while in men, it lies at the rim. The medial and lateral ends of the eyebrow should lie at the same horizontal level. In general, the ideal shape of the brow has been described with the crest of the arch over the lateral canthus, with some aesthetic refinement based on each patient's facial shape [82]. The position and shape of the brow is a dynamic balance between elevator and depressor forces. The frontalis muscle is the only brow elevator and is opposed by the *orbicularis oculi*, *depressor supercilii*, *procerus* and *corrugators supercilii* muscles. As time passes, the shape and vertical position of the brow changes as muscles weaken and the forces of gravity take hold. The aim of the treatment is to lift the lateral eyebrow. The medial aspect could also be lifted in selected cases. Eyebrows can be elevated by injection of the depressors and allowing elevators of the brow to act unopposed. We describe here three techniques that could help the practitioner in achieving this result.

The first technique is suitable for mild lateral eyebrow lifting when the opponent elevating lateral fibers of the frontalis muscle are strong enough to produce the lifting effect with the antagonist blocking. One injection is placed into the upper lateral fibers of the orbicularis oculi pars orbitalis muscle approximately 0.5cm above the orbital rim. The recommended dose range is 3-4U of onabotulinumtoxinA and 10-12U of abobotulinumtoxinA per point of injection (Figure 8) [83-88].

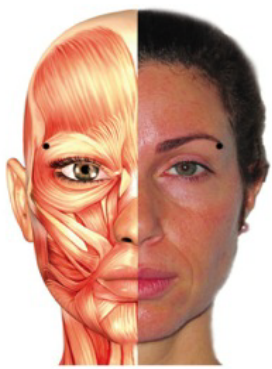

**Figure 8:** Injection points for brow lift (Technique 1).

The second technique is generally used when only the lateral aspect of the eyebrow needs elevation and there are not many horizontal fibers in the forehead, only in the midline. It consists of the full blocking of the medial fibers of the depressors and partial blocking of the medial fibers of the frontalis muscle. Seven injections point are made (FIG X) treating the corrugatores muscles with a dose range of 3-5U of onabotulinumtoxinA (10-15U of abobotulinumtoxinA) per point, the procerus muscle with 3-5U (10-15U of abobotulinumtoxinA) and the medial frontalis muscle fibers with 2-6U (6-15U) in two points (Figure 9) [83].

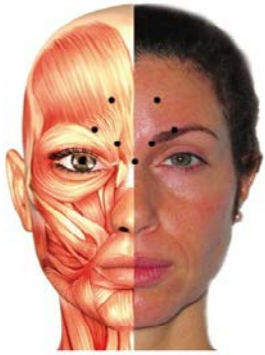

**Figure 9**: Injection points for brow lift (Technique 2).

The third technique is the most appropriate for medial, intermediate and lateral eyebrow lifting and it consists of the use of three to five injection points within the hair of the eyebrow. The injections should be superficial, with the needle pointing upwards and located approximately 0.5cm above the bony orbital rim to avoid intraorbital diffusion of botulinum toxin A. For lateral lifting only, three points are injected laterally to the supra-orbital foramen at the hemipupillary line. The dose range is of 10-15U of onabotulinumtoxinA and 30-40U of abobotulinumtoxinA divided between the three sites over the supero-lateral portion of the orbicularis oculi muscle [83-88]. If medial and lateral eyebrow lifting is desired, the toxin should be distributed in five injections sites within the whole eyebrow (Figure 10).

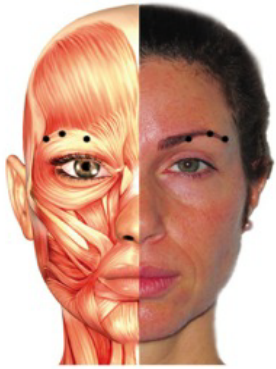

**Figure 10:** Injection points for brow lift (Technique 3).

**Complications:** The main concern when injecting the orbicularis oculi muscle is the risk of diffusion of botulinum toxin to surrounding muscles. Diplopia can occur when the lateral rectus muscle is reached by diffusion, eyelid ptosis when the levator palpebri muscle is reached or excessive brow elevation when the frontalis muscle is caught by diffusion [89]. The third technique aforementioned may lead to upper eyelid ptosis if the toxin is injected too deep and the needle directed downwards. Sculpting of the lateral brow with BTX-A is unpredictable in the amount of elevation achieved in each individual with a given dose. Using a conservative dose with reinjection in 2 weeks is a safe and controlled manner of addressing this problem.

## Orbicularis oculi/Crow's Feet

The aging process in the eye area may lead to skin excess, eye bags, static and dynamic

wrinkles and pigmentation disturbances. The wrinkling is usually noticed when smiling and localized at the lateral part of the lower eyelid. Static wrinkles are caused by skin photo-damage and could be present in young people. Eyelid wrinkling may also result from the desiccating effect of wind and from smoking. Patients with light-colored eyes are more sensitive to daylight and as a consequence, squinting in bright sunlight may mechanically contribute to the lateral periorbital wrinkles. Patients with thick skin present deeper wrinkles and the more atrophic the skin is, the greater the quantity of fine wrinkles that may be found. Moreover, eyebrow ptosis may contribute to upper lid excess and skin wrinkling. The orbicularis oculi muscle functions for voluntary and involuntary closing of the eyelids. Periorbital rhytids, or crow's feet, result from the hyperkinetic sphincter function of this muscle. Its lateral portion has direct dermal insertion, which creates fine senile wrinkles in a radial pattern. The aim of the treatment with BTX-A is to weaken the sphincter contraction of the orbicularis oculi so to soften the skin lines and yield a refreshing appearance to the eyes. The precise location and depth of injection is very important to avoid possible complications such as lid or lip ptosis. As we know from the anatomy, the *zygomaticus* major and *levator labii superioris* muscles blend with the deep surface of the orbicularis oculi muscle, and together serve to elevate the upper lip and oral commissure. Chemodenervation of these adjacent muscles could lead to lip ptosis [89,90]. To avoid this complication, a careful selection of injection sites is mandatory. Good lighting and stretching the skin may help the practitioner in avoiding perforating blood vessels that could lead to bruising and ecchymosis. Injection points are usually three to five and are located based on observed muscle action and superficial landmarks. Care should be used to inject along an arc 1cm from the lateral and inferior bony rim in order to mitigate the risk of intraorbital diffusion and inadvertent lid ptosis [55,91]. As the periorbital skin is thin, the needle must be inserted almost parallel to the skin and the botulinum toxin will diffuse to the underlying muscle; with deeper injection, it is more likely to produce skin bruising. The total starting dose is typically 12U of onabotulinumtoxinA [92] or 30U of abobotulinumtoxinA [93], divided equally per injection site (Figure 11). Injecting into the periorbital area is also useful for lifting the lateral aspect of the eyebrow. For this reason, in common practice, a combined treatment of glabellar lines, periorbital rhytids and a subtle temporal brow-lift is given in a single session (Figure 12-17).

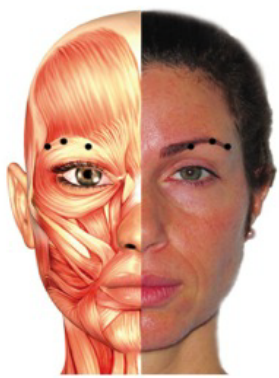

**Figure 11**: Injection points for crow's feet treatment.

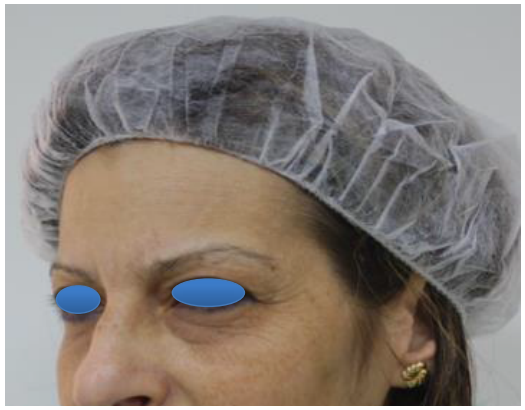

**Figure 12**: Pre-treatment.

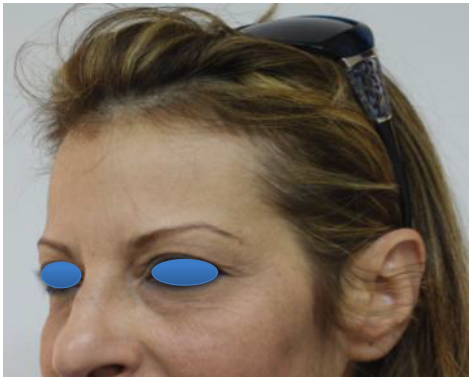

**Figure 13:** Post treatment (forhead, glabellar, and periocular – Vistabex 50 U).

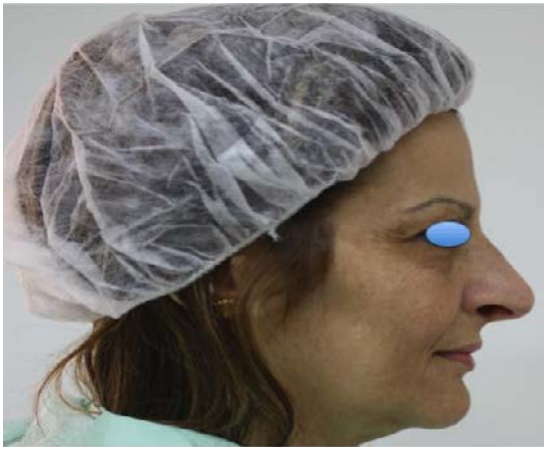

**Figure14:** Pretreatment lateral view.

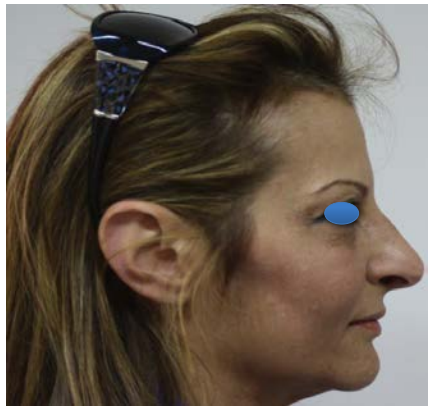

**Figure 15:** Post treatment lateral view (3 months).

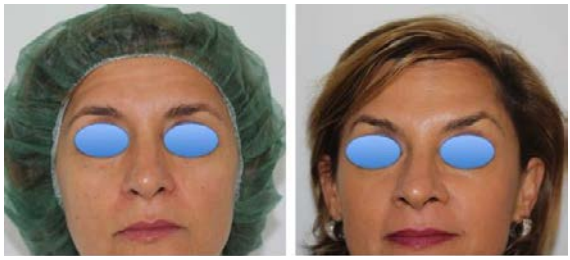

**Figure 16:** Pretreatment - On the left; Post-treatment (forehead, glabellar, and periocular - Vistabex 50 U) 3 months - On the right.

**Figure 17:** Pretreatment - On the left; Post-treatment (forehead, glabellar, and periocular - Vistabex 50 U) 3 months - On the right.

## Lower eyelid

When observing the lower eyelid care should be taken to check for the quality of skin, presence of eye bags and wrinkling. Eye bags may result from the laxity of the orbicularis oculi and are considered to be pseudo-herniation. It is not advisable to inject botulinum toxin in patients with prominent eye bags; surgery would be the best option in these cases. The skin wrinkling in the lower eyelid results from the hyperkinetic behavior of the palpebral portion of the orbicularis oculi muscle. The pretarsal portion of the muscle may produce orbicularis hypertrophy which reduces the palpebral aperture. Injecting BTX-A would soften

the bulging at this site and promotes eye widening. A “snap test” to measure lower lid skin laxity should be performed because a poor response can be expected if the skin does not snap back into place after downward tugging [94]. The best injection site in the lower eyelid is at the pretarsal in the midpupillary line and as well as improving lower eyelid wrinkling, it produces a widening of the eye which leads to aesthetic enhancement. A microinjection technique for one to two injection points is recommended. The needle should be inserted parallel to the skin so that a very superficial papule is seen. The total dose should be 1-2U of onabotulinumtoxinA or 2-4U of abobotulinumtoxinA (Figure 18) [95,96]. Treating the lower eyelids is not for the novice injector, due to the delicacy of this area, but is effective with experience and reasonable skill [67].

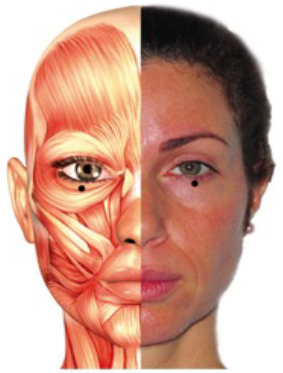

**Figure 18**: Injection points for lower lid treatment.

**Complications:** Care should be taken to avoid injecting patients with dry eyes, morning eyelid edema or poor skin elasticity. All patients should have a positive “snap test” [94]. Patients with with skin excess, eye bags, sclera show, static and dynamic wrinkles and pigmented spots will not be 100% satisfied with the use of botulinum toxin A and they will tend to see only the negative aspects of this treatment. Ecchymosis and bruising may result from injection into the lower eyelid or deeper injections at the crow’s feet. Use of ice bags is recommended. Upper lip asymmetry or cheek ptosis may result from injecting into the lowest extensions of the crow’s feet at the zygomaticus major muscle. Usually these complications result from injecting too deep [89,90]. Similar to the treatment of the frontalis muscle, the goal should be to weaken the muscle rather than cause complete immobility since excessive blocking of the palpebral portion may affect the lacrimal pump mechanism, forced eyelid closure and the blink reflex. This may lead to dry eyes and corneal exposure especially in older patients. When injecting the lower eyelid care should be taken to inject in the midpupillary line because lateral injections to this point would lead to eyelid ectropion and rounded lateral canthus, whereas medial injections may cause epiphora and dry eyes. Moreover, excessive blocking of the palpebral portion of the orbicularis oculi may lead to impairment of eye closure, for both voluntary and involuntary functions [96,97].

## Perinasal lines/ Bunny lines

The perinasal or bunny lines are wrinkles that fan over the nasal dorsum and sidewalls from hyperkinetic function of the nasalis muscle, seen predominantly in patients with thin skin. These lines may be naturally present in some patients during animation like smiling, laughing, frowning and even speaking. They may appear or become more prominent after treatment with BTX-A, especially when the glabella and crow’s feet are treated, leading to the so-called “Botulinum Toxin sign”. This is due to the fact that in some patients when

the frontalis, the corrugatores, the procerus and the orbicularis muscles are blocked with botulinum toxin injections, the untreated nasalis muscles react with over-contraction being itself a synergistic muscle when the eye and nose complex is under animation, therefore leading to wrinkle formation. Observed muscle action is considered most important for locating injection points. During animation, patients should be asked to laugh, to sniff and to squint intensely. Injections are placed in an intramuscular plane centered over each nasal bone medial to the nasofacial junction, which corresponds to the bulk of the nasalis muscle. It has to be paid attention not to inject too close to the nasofacial junction so the botulinum toxin does not spread laterally to the *levator labii superioris alaeque nasi* muscle and cause lip ptosis (Figure 19). Care should be taken with blood vessels at this level; otherwise bruising may result, so stretching the skin to identify blood vessels prior to injection and slight pressure after injection is recommended. One injection site on each side is used to treat the "bunny lines". A total dose of 2-5U of onabotulinumtoxinA or 6-15U of abobotulinumtoxinA should be distributed on both lateral sides [67,98,99].

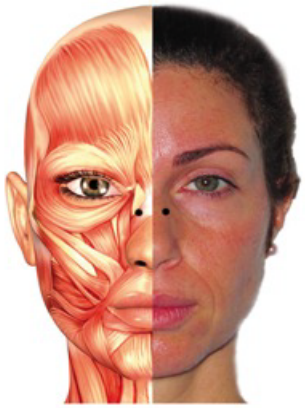

**Figure 19**: Injection points for Bunny Lines treatment.

**Complications:** As aforementioned it is important not to inject too laterally down the nasal sidewalls otherwise the levator labii superioris alaeque nasi may be blocked and upper lip ptosis and asymmetry could result. The most common complication is the presence of ecchymosis or hematoma due to injection into the angular vessels [9]. Diplopia may occur from inadvertent blocking of the rectus inferior or medialis.

## Gummy Smile

Gummy smile is defined by having an excessive gum line exposure with a full smile where the gingiva above the canines can be seen. Patients with a short distance between the nasal base and Cupid's bow as well as those with a facial convex profile with a prominent nose and underdeveloped chin are prone to exhibit this kind of smile. Deep nasolabial folds are also found in these patients. The levator labii superioris muscle that elevates the upper lip and the *levator labii superioris alaeque nasi* muscle that elevates the medial part of the upper lip and the nasal flare are responsible for the gummy smile [100]. As a matter of fact, in patients with gummy smile it is very common to see the inversion of the upper lip when smiling which makes these patients usually bad candidates for upper lip augmentation with fillers only. The ideal treatment would be a combination of filler and botulinum toxin. As the golden proportion establishes, that the upper lip should cover the upper third of the central incisors, the aim of treating gummy smile with botulinum toxin is

to avoid gingiva showing at rest and to reduce excessive gum exposure during a smile. The patient should be asked to smile at maximum contraction, then two injection sites on each side of the face are given. Both are deep intramuscular injections but remain superficial to the periosteum. The first injection site is at the nasofacial junction for treatment of the alaeque nasi muscle. The second site is approximately 2cm inferior to the bony orbital rim just medial to the midpupillary line for treatment of the levator labii superioris muscle (Figure 20). Care must be taken to not weaken the zygomaticus major muscle by placing the injection too lateral over the malar eminence. A starting dose of 2U of onabotulinumtoxinA or 5U of abobotulinumtoxinA per side is recommended. After 15 days the patients should be evaluated and treated if necessary [9].

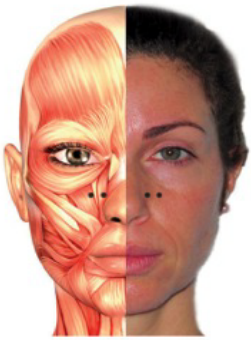

**Figure 20**: Injection points for Gummy Smile treatment.

**Complications:** Asymmetries and upper lip drooping are the most common complications. Asymmetries should be corrected with administration of 25% of the initial dose and the outcome evaluated after one week. Excessive drooping of the medial part of the upper lip may happen if excessive blocking is undertaken, resulting in the "joker" smile due to excessive lateral pulling of the zygomaticus major muscle [98]. In order to reduce the possibility of complications the ideal candidate would be a patient with the open lip posture and with a short upper lip. Even if excessive upper lip elongation results, it will benefit the patient.

## Nasal tip

The tip of the nose plays an important role in nasal beauty. Aging process leads to the drooping of the nasal tip accentuating any dorsal convexity of the nose. A ptotic or drooping nasal tip may result, in younger patients, from overactivity of the depressor septi nasi muscle and can be exacerbated by smiling. These patients usually present a drooping nasal tip and upper lip shortening when smiling, with a convex shaped face, prominent nose and underdeveloped chin. The patient should be evaluated according to the length of the upper lip and the nasal-labial angle before injected. Superficial landmarks are of the most importance. There are two ways of injecting the depressor septi nasi muscle: through the skin and intraorally [45,101-103]. The nasal area is quite sensitive so the use of topical anesthesia or ice bags to reduce the pain is recommended. The authors prefer the transcutaneous approach since the intraoral approach may present some difficulties to inject into the correct level. The injection points are marked at the base of the columella at the medial crural footplate. Two points are marked, one at each side of the medial crura (Figure 21). The injection should be superficial, inserting only the first third of the needle. The dose at each side is 1-2U of onabotulinumtoxinA or 4-6U of abobotulinumtoxinA [67]. The dose is adjusted based on desired degree and duration of correction, facial proportions, observed muscle action and adjacent muscle function.

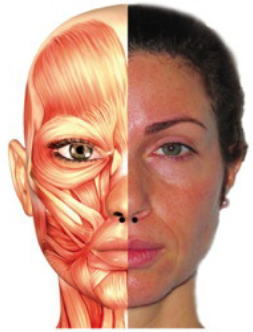

**Figure 21**: Injection points for nasal tip treatment.

**Complications:** Complications are rare if patients are selected properly. Pain is the adverse event most often reported. Over-blocking of the depressor septi nasi muscle may result in upper lip ptosis which may lead to the "joker" smile because of the action of the zygomaticus major muscle.

## Perioral/lip rhytids

When aging the lip undergoes a typical series of changes includes the recession of the lateral lip, an increase in the upper white lip length, thinning of the vermillion bulk and dense vertical rhytids radiating around the mouth. These rhytids may also be called "smoker's lines" and can result from environmental influence such as smoking and photodamage, hereditary factors and habitual hyperfunction of the orbicularis oris muscle sphincter (musicians) [9,67]. Wrinkles of the upper lip are often treated by multiple modalities such as with fillers or resurfacing [104-106], but BTX-A can aid in improving the appearance of the perioral area, and becomes especially indicated when deep and static rhytids around the mouth and lips are present. The lip sphincter should be treated conservatively in order to efface deep oral wrinkles without compromising oral competence. The patient is asked to pucker and the wrinkles are marked. Care is taken to avoid injecting around the commissure because the toxin may diffuse and weaken the lateral lip elevator muscles, resulting in lip ptosis and drooling [98,107]. Injecting the midline should also be avoided to prevent effacement of Cupid's bow reducing the landmarks of a perfect lip. In general, four sites are treated, one or two injections per lip quadrant. Very small doses should be used in order to avoid dysfunctional mouth. The injections should be placed 5mm from the vermillion border in order to obtain a nice secondary effect of lip eversion. Inexperienced injectors should start injecting each lip quadrant with a total dose of 0.5U of onabotulinumtoxinA or 2U of abobotulinumtoxinA in an intramuscular plane to avoid complications of overtreatment (Figure 22) [67,98].

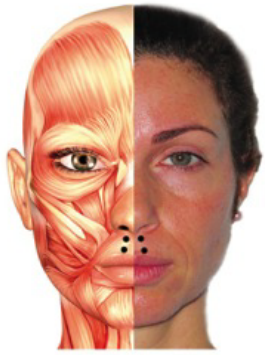

**Figure 22:** Injection points for the treatment of perioral rhytids.

like inability to purse or maintain an embouchure, mild articulation difficulties with plosive consonants and difficulties in eating and drinking. Therefore, injections should be started with low doses and repeated as necessary to avoid oral incompetence or unwanted asymmetries [9].

## Marionette lines

Marionette lines appear as deep folds, angled downward, that develop from the corners of the mouth and lower lips, which might give the total face an expression of being dissatisfied, sullen or even scornful. A combination of factors could lead to the formation of these folds like the loss of dermal collagen, fat atrophy and redundant or ptotic skin, all of which could be addressed by surgery or injectable fillers. In some cases these folds could also be deepen with time by the over-activity of the depressor anguli oris muscle due to its dermal attachments and downward pull of the corners of the mouth. Botulinum toxin could be useful in weakening this muscle allowing the zygomaticus major and levator anguli oris muscles to lift the corner of the mouth back to a horizontal plane. In some patients the activity of the platysma muscle, which interdigitates with the depressor anguli oris muscle, may contribute to the deepening of the marionette lines; therefore, a treatment of both muscle groups can be helpful. The best result in selected patients is seen with the combination treatment of Botulinum toxin A and fillers, the first enhancing and prolonging the duration of the effect of the latter [107]. The patient is asked to grimace and show their bottom teeth in order to identify and palpate the depressor anguli oris muscle as well as additional platysmal bands. Usually two points per side are injected, one that targets the depressor anguli oris and the other one that targets the platysmal bands inserting at the lateral parts of the orbicularis oris muscle. Injection around the oral commissure or medial lower lip is avoided to prevent inadvertent weakening of the orbicularis oris or depressor labii inferioris muscles. It is recommended to keep a distance of at least 1cm from the corners of the mouth of the patient and the first point of injection can usually be found, after palpation, in the elongation of the naso-labial fold. Another injection point should be put more laterally in the area of the mandible in order to target the platysmal bands (Figure 23). Injection should be done in an intramuscular plane. Some authors place one single injection on each side no more than 1 cm above the inferior mandible rim in a line parallel with the oral commissure [9]. The recommended initial dose is 2-5U of onabotulinumtoxinA or 10U of abobotulinumtoxinA per injection point with adjustments made based upon each patient's muscle mass [9,67].

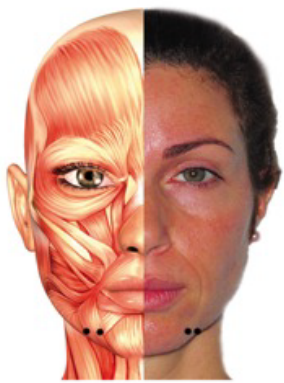

**Figure 23**: Injection points for Marionette Lines treatment.

**Complications:** Over treatment or injecting too close to the corner of the mouth may lead to asymmetry, oral incompetence such as drooling and articulation problems.

## Cobblestone chin

Cobblestone chin, also known as pebbled, dimpled or golf ball chin develops when the mentalis muscle, which inserts with several fibers in the dermis of this area, is contracted. A combination of processes contributes to the deepened chin convexity and orange-peel appearance of the skin seeing with aging, very similar to what happens with the perioral rhytids and the melomental fold. Weakening of the mentalis muscle can soften the mental crease and improve some of the skin dimpling not attributed to loss of dermal collagen. The patient is asked to contract the chin by pulling the lower lip down. The botulinum toxin A can be either injected in one single point or in two lateral points, one on the left and one on the right side, approximately 1 cm from the midline and just superior to the mental tubercle. No injections points should come closer than 1 cm of the lower lip. The mentalis muscle is the deepest muscle in this region, so intramuscular injection just above the periostium, as well as inferior to the crease, will avoid undesired oral incompetence and articulation problems from weakening of the oral sphincter and depressor functions. Some authors refer that, although the muscle is quite deeply located, superficial injections are fine and will lead to quite satisfactory results (Figure 24) [109]. The recommended total dose range is 2.5-8U of onabotulinumtoxinA and 2.5-20U of abobotulinum toxin A [9,67].

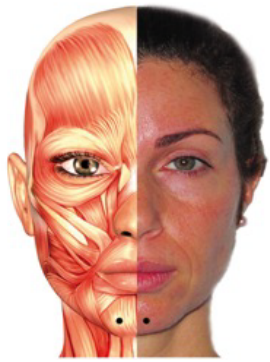

**Figure 24**: Injection points for Cobblestone Chin treatment.

**Complications:** Respecting the appropriate distance from the lower lip leads to no complications apart from bruising or hematoma. Injecting too close the lower lip may involve the depressor labii inferioris which would lead to a dysfunctional mouth with ptosis of the lower lip.

## Platysmal Bands

Changes of the neck, when aging, can be caused by excessive skin laxity and loss of elasticity, jowl formation, lipodystrophy, submandibular gland ptosis and bone resorption [110,111]; the platysma muscle can become hyperkinetic, lose tone and be dehiscent in some areas, all of which contribute to the so-called turkey neck appearance. In the anterior neck, the platysmal muscle separates from the contralateral side forming vertical bands that become more visible with forceful contraction, whereas in the lateral neck, additional bands develop around areas of weakened muscle tone and dehiscence [112]. Treatment with botulinum toxin A may soften the prominence of these bands when contracted. Furthermore, lateral cheek lines and marionette lines can be improved when reducing the strength of the platysmal bands. Patient's selection is very important in these kinds of patients; kinetic or hyperkinetic patients who contract the platysmal bands actively when

speaking are best. Patients must be in a sitting position because this helps the active contraction of the platysma muscle. Patients are asked to grimace. Treatment follows the course of the contracted bands. Four to eight injections points (depending on the length of the band) are placed for each band approximately 1.5cm from each other. Grasping the band with the non-injecting hand might be helpful while injecting the contracted muscle in an intradermal plane (Figure 25). A conservative initial dose is recommended, using 2U of onabotulinumtoxinA or 5U of abobotulinumtoxinA per point [67]. Care must be taken to avoid deep injections or overdosing.

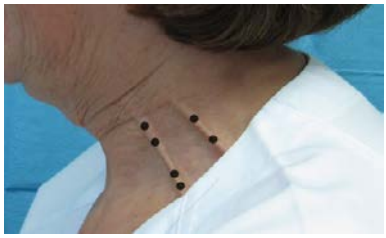

**Figure 25**: Injections points for platysma treatment.

**Complications:** Bruising is quite common also because pressure after the injection should only be applied carefully. The pharynx region should be spared from injecting because of the risk of diffusion of the toxin to the underlying muscles which may lead to difficulty swallowing, neck weakness and dysphonia [113,114].

BTX-A is not treatment for horizontal neck lines, other methods might be more appropriate, such as the combination of fillers and ablative procedures. Treatment of platysmal bands might become quite expensive due to the numerous injection points. Patients should be informed about this before starting the treatment [115,116].

## Post-Treatment Care

Gentle pressure with or without cold compresses can be applied to the treated site immediately after each site is injected, if ecchymosis and erythema result as an immediate complication. Some authors suggest that the patient should be advised to actively contract the treated muscle in attempt to enhance toxin uptake by causing more rapid internalization of the toxin, but this has not been proved yet [11]. Patients are told to go back to normal life immediately after their session but are advised to avoid lifting, bending or straining for the 3 to 4 hours, particularly when the treated site is in the upper third of the face, to help prevent unwanted spread of the toxin. Flying and heat exposure do not have an adverse impact. Makeup is unrestricted. Non-aspirin products can be given if the patient complain of headaches and it's important to advise the patient not to take any drug or supplement that could interfere with coagulation in the 10 to 14 days after treatment in order to help prevent ecchymosis. Patients are told to return for a post injection examination after 2 weeks if they suspect a therapeutic failure or are not completely satisfied with the result. Otherwise, patients are advised to return after 3 to 4 months for additional treatment if they want to maintain the result.

## Combination Treatments

In common practice Botulinum toxin A is usually injected alone, although it could be used in combination with other treatments, during the same or susequent session, to treat the different layers of the skin and various conditions. In the last few years one of the

most important changes in facial rejuvenation has been a shift from a two-dimensional focus on hyperdynamic facial lines and immobilization of corresponding muscle to an increased comprehension and appreciation of the three-dimensional aspects of facial aging, particularly the loss of volume and its effect on treatment approaches [117]. This has changed the way Botulinum Toxin A is used in clinical practice. Practitioners now tend to treat not only one single area of the face but multiple areas to provide a more natural and relaxed look [118,119]. Moreover, BTX-A is everyday more often used in combination with other modalities, including dermal fillers. When BTX-A is used in combination with fillers, it becomes possible to address facial rejuvenation from a three-dimensional rather than a two-dimensional approach, providing more pleasing, longer-lasting aesthetic outcomes [107]. When botulinum toxin is combined with filler, it tends to prolong the longevity of the filler by decreasing the metabolism in the surrounding tissue. BTX-A may be injected into the frontalis muscle on the upper part of the forehead (1 to 2cm above the brow) and a filler can be injected in this lower area of the forehead in order to efface the residual static lines of the entire forehead [120]. The same can happen when treating deep glabellar lines; a combination of toxin and fillers may be necessary to achieve an optimal result [121]. When treating the orbicularis oris muscle, the better aesthetic outcome of treating the vertical lip lines or the lip itself with fillers in combination with BTX-A become immediately evident. It is said to be the perfect treatment for male patients because of the depth of the male wrinkles [107]. Botulinum toxin and fillers can be safely used at the same time because one procedure does not interfere with the other because both are injected into different layers. Usually, the toxin is injected first and the filler soon after [116]. When botulinum toxin is combined with laser resurfacing, it has the potential to enhance the effect by improving collagen reorganization while the skin is paralyzed [122]. Great results are seen when botulinum toxin is used in combination, but not simultaneously (the injection of the toxin should be performed 1 or 2 weeks before the procedure), with laser resurfacing of the lower lid or the lip [123-125]. Regular postoperative injections every 4 to 6 months prolong and expand and refine the laser resurfacing procedures [126]. Botulinum toxin can be used together with chemical peels, especially in patients with photodamaged skin due to excessive sun exposure [122]. While the toxin treats the dynamic wrinkles, the chemical peels treat superficial skin wrinkling and pigmentation. BTX-A treatment is also successfully used in combination with various surgical procedures such as surgical brow lift allowing for greater stability of brow elevation, upper and lower eyelid blepharoplasty and rhytidectomy enhancing the results and prolonging the aesthetic outcome.

**Complications:** Botulinum toxin is a very safe drug when used appropriately. As the effects of the toxin begin to wear off in 10-12 weeks post-treatment, any undesired results are ultimately self-limited [127]. Irreversible medical complications are not known. There are three general categories of complications: local, regional and systemic.

The most common transient local complications are self-limited adverse reaction at the injection site that typically subsides within a few days without treatment. These include injection site pain, bruising, swelling, erythema, edema, ecchymosis, tenderness, headache and short term hyperestesias [72,73,128]. Headaches are usually mild and last a few hours and are attributed to the initial muscle spasm caused by the toxin in the first 12 hours, followed by muscle weakness for months thereafter [9].

Regional complications are adverse events caused by local diffusion of the toxin into areas not meant to be treated. Some of those have been previously described in previous sections. One of the most feared regional complications is blepharoptosis which is due to the diffusion of the toxin into the levator palpebrae muscles after treatment of glabellar lines or periorbital rhytids [90,93,129]. Ptosis can occur as early as 48 hours or as late as

7 to 10 days post-treatment. Proper technique is the best means to avoid this complication, injecting 1cm superior to the orbital rim and use of the non-dominant index finger to support the desired muscle mass without deep injection through or near the orbital septum [45]. Apraclonidine, an alfa2-adrenergic agonist, can be used to decrease the severity of lid ptosis by stimulating the Mueller's muscle; an elevation of 1 to 3mm can be obtained in this manner [77-80,116]. Brow ptosis is another complication that can occur more often in older patients and can be avoided with proper technique [9,67]. Ectropion can be caused by injections placed around the lower lid affecting the function of the orbicularis oculi muscle [95]. Strabismus have been described after misplaced lateral (crow's feet) or medial (bunny lines) periorbital treatment due to the diffusion of the toxin to the rectus lateralis muscle [55,91]. Other regional complications include dysphagia from platysma muscle injection or loss of facial expression (mask-like face) from excessive paralysis [111,113,114].

Systemic reactions can include nausea, fatigue, malaise, flulike symptoms, distant rashes, respiratory arrest and death. Botulinum toxin is not expected to be present in peripheral blood at measurable levels following intramuscular injection when therapeutic doses are used. Generalized adverse events are reported very rarely in aesthetic medicine, where only very low doses of the toxin are given. In fact, most of the literature on complications is from non-cosmetic sources. Depending on the dose and the number of muscle injected, the onset of systemic reactions typically occurs within 1 week and they continue for 1-2 weeks. Typical effects of systemic action would include dry mouth, red eyes, accommodation disturbances and gastrointestinal symptoms [59,67,77,79,80,130]. The patients at greatest risk are children treated for muscle spasticity disorders, such as cerebral palsy, even in doses comparable to those used to treat cervical dystonia [9].

## Immunogenicity

Immunologic complications include acute type I reactions and may be attributable to human serum albumin. These may occur in patients treated with large volume of toxin since the development of IgG neutralizing antibodies against the toxin seems to correlate with an increasing number of injections and the total cumulative dose thus leading to a decreased efficiency due to an inactivation of the toxin itself [132]. In aesthetic medicine, where usually very low doses are used, the problem of antibodies seems to be of little concern [67].

## Nonaesthetic Uses for Botulinum Toxin

The principal therapeutic aim of any kind of condition involving treatment with botulinum toxin is to reduce undesired or excessive contraction of striated or smooth muscles. Since its very first successful experiments on animals in ophthalmology [133], the use of botulinum toxin has increased exponentially throughout the spectrum of medical specialties. It is used with success for the treatment of many neuromuscular conditions and it's recognized to be a first-line therapy for focal dystonias [134,135]. In the (Table 2) there are some examples of the numerous applications for botulinum toxin [136-151]. Many other potential uses of botulinum toxin in medicine are yet to be discovered.

| Partial List of the Use of Botulinum Toxin in Medical Terapy | | | |
|---|---|---|---|
| Achalasia | Dental procedure | Hyperhidrosis | Reduced appetite |
| Anal Fissure | Esophagel stricture | Inner ear disorder | Spinal cord injury |
| Back pain | Essential tremore | Neck pain | Strabism |
| Bening prostatic hypertrofy | Following Mhos microsurgery repair | Massateric muscle hypertrofy | Temporomandibular joint disfunction |
| Blepharospasm | Facial spasm | Overactive bladder | Teet grinding |

| | | | |
|---|---|---|---|
| Brest reconstruction and augmentation | Gustatory sweating (Frey's syndrome) | Poststroke limb spasticity | Vasospastic disorders Vocal cord disorders |
| Cerebral palsy | Facial nerve disorder | Parotid fistulas | Tourette's syndrome |
| Cervical dystonia | Hedaches | Pressure ulcers | Wound healing |

**Table 2**: Non cosmetic applications for Botulinum Toxin in medicine [11].

## Conclusion

Minimally invasive aesthetic procedures have grown exponentially in number in the last several years. Botulinum toxin A, is a mainstay of facial rejuvenation and its use is an 100% effective procedure. It is absolutely safe when used at therapeutic dosage. A very important point that has to be perfectly understood is that botulinum toxin A formulations are not interchangeable, therefore the practitioners must learn how to use each product properly to provide optimal and safe outcomes for their patients. The new concepts of aging and rejuvenation have moved towards an appreciation of the three dimensional aspects of aging, including the contribution of volume loss to appearance. For this reason the overwhelming trend is toward increased combined use of botulinum toxin A and hyaluronic acid fillers as well as other modalities such as resurfacing, to provide a more balanced and harmonious aesthetic result and at the same time increasing the longevity of the outcomes. The primary aesthetic use of botulinum toxin remains in the face and neck, being the treatment of glabellar lines the only use approved and all the other uses considered off-label. The potential uses of botulinum toxin in aesthetic and non-aesthetic medicine are numerous and in continuous development.

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## Chapter 8

# Biostimulation: Platelet Rich Plasma

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## Indications

Platelets have long been known for their role in early hemostasis, while their tissue regenerative properties have been discovered only over the last decade [1-3]. Recent studies have shown that platelets intracellular granules contain hundreds of active cytokines and growth factors, all critical during tissue healing and regeneration (Table 1) [4]. By isolating and concentrating platelets through centrifugation it is possible to concentrate the growth factors and deliver them in a specific area where biostimulation is needed. The highly concentrated growth factors stimulate endothelial cells and fibroblasts to proliferate and differentiate leading to angiogenesis, new collagen deposition and contraction [1]. In addition, platelets stimulate the recruitment and differentiation of mesechymal stem cells.

Although the use of Platelet Rich Plasma (PRP) is increasing in cosmetic surgery, clinical high level evidence of PRP's efficacy is still lacking, being at times still based on anecdotal reports, individual surgeon opinions or marketing strategies.

By analyzing the literature, it appears that PRP has been employed in several cosmetic applications since a few decades. Described PRP cosmetic applications include decreasing facial rhytids, decreasing hematoma/seroma post rhytidectomy [5], stimulating hair growth [6,7], enhancing the taking rate of fat transplant [8,9], stimulate collagen production in the subcutaneous tissues when used as a filler (alone or combined with collagen or ialuronic acid), and improving the appearance of stretch marks and scars (alone or in combination with laser) [10].

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|---|
| • VEGF |
| • PDGF-a and b |
| • TGF- a and b |
| • EGF |
| • IGF |
| • Osteocalcin |
| • Osteonectin |

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|---|
| • Fibronectin ( and fibrinogen) |
| • Thrombospondin |

**Table 1:** Secretory proteins and growth factors released by activated platelets in platelet rich plasma.

### Pre-treatment evaluation

Patients should be screened for coagulation problems such as hemophilia, coagulation factor deficiencies, dyscrasias. Any platelet deficiency or significant increase should be investigated prior treatment. In addition, patients should not be under medications affecting platelet function, such as aspirin or clopidorgrel, or their use should discontinued at least 15 days prior treatment [11].

### Pearls

A key issue has traditionally been PRP delivery method. In particular, whether PRP should be activated (with calcium and thrombin) and transformed into a gel or not. Once PRP is activated it becomes a gel and platelets degranulate, releasing their content rich in growth factors in a bolus [1]. Recent evidence has shown that platelets within the PRP can act as an "intelligent" drug delivery system when PRP is not activated, rather than acting as concentrating vectors for growth factors [1]. Intact platelets induce a sustained release of growth factors over time in the site of injection. Non-activated PRP is then considered as a cell therapy, while activated PRP is a growth factor treatment [12].

### Technical points

Whole peripheral blood is collected into a citrate containing tube. The tube is kept at room temperature (21-24 ˚C) and constantly gently shacked to prevent platelets from aggregating (if some time passes between collection and preparation, a rocker can be used).

The blood is then centrifuged for 5 minutes, at a 1500 g (RCF centrifugal force) [1]. A key important feature of the centrifuge is the brake, the machine should be able to slow down at the end of the cycle slowly as too rapid stop would cause platelets to deposit into the buffy coat, making their harvest more difficult. This method of preparation allow for a collection of quiescent, non-activated platelets as opposed to harsher methods (higher centrifuge speeds), which partially activate or destroy the platelets.

The tube is then kept vertical and platelet rich plasma can be noted on the top as a translucent or turbid, yellowish layer, which stands on top of a thin white layer (the buffy coat, rich in white blood cells) and a higher red layer on the bottom (red blood cells). The top part of the platelet rich plasma should be withdrawn with a syringe and a large bore needle paying attention not to aspirate and mix it with the other cell layers. Following these instructions it is usually possible to obtain platelets concentration between 2 and 3 times over whole blood levels. Many commercial PRP preparation kits exists, using which it is possible to have ready to use PRP with concentrations up to 8 times blood concentrations without having to worry about all the above technical aspects.

Once obtained, PRP is injected using a syringe and a small caliber needle (i.e. 30 Gauge) when in its liquid form or rather a larger one 16-18-gauge catheter if in the gel form in the desired area of treatment. Spray systems are also commercially available to deliver a liquid spray that becomes a gel once on the wound bed.

## Indications

Decreasing facial rhytids, decreasing hematoma/seroma post rhytidectomy, Stimulating

hair growth, enhancing the taking rate of fat transplant, stimulate collagen production in the subcutaneous tissues when used as a filler (alone or combined with ialuronic acid), and improving the appearance of stretch marks and scars (alone or in combination with CO2 laser).

## Pitfalls

If the PRP is prepared without the use of a commercial kit it is important to test the final product in terms of platelet concentrations until the protocol reaches the desired levels of reproducibility. In this case, whole blood and the PRP of the patient are sent to the laboratory to make sure platelets concentrations are above whole blood levels [13].

PRP, by definition, does not contain inflammatory cells and erythrocytes, and the presence of these cells may influence the overall results: careful manipulation of the sample after centrifugation should prevent any mixing of the layers. After the centrifugation step, if the top layer is citrine yellow and not turbid, it is likely that the vast majority of platelets are deposited in the buffy coat, making platelet harvest almost impossible without taking some of the buffy coat and the red blood cells as well.

If higher volumes are obtained that what needed, it has been suggested to freeze the PRP for later use. Freezing PRP may preserve the growth factor content, but induces “cold damage” on the platelets meaning that platelets will not be functional cells anymore, but just terminally activated cytoplasmatic fragments. [12]

## Post treatment care

PRP injections usually do not need any specific post treatment care. Since the majority of the procedures involve subcutaneous injections, cold packs are recommended in order to decrease pain and swelling on the site.

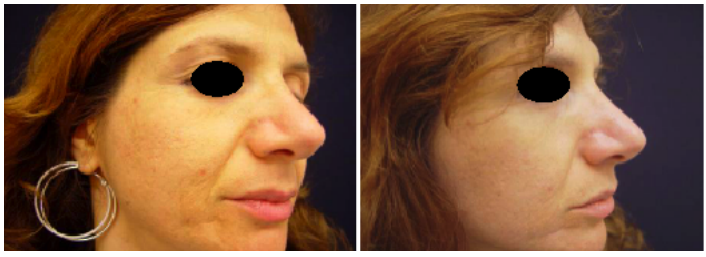

**Figure 1:** Pre and six months post treatment.

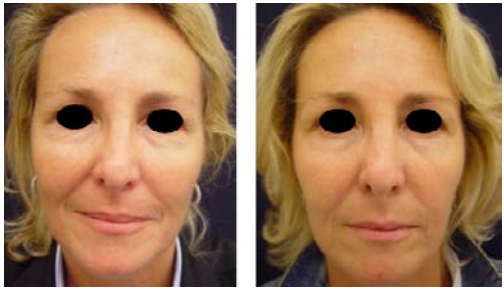

**Figure 2:** Pre and six months post treatment (frontal view).

**Figure 3:** Pre and six months post treatment (lateral view).

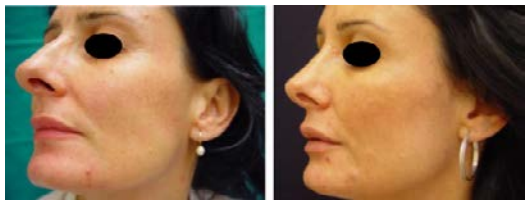

**Figure 4:** Pre and six months post treatment (lateral view).

### Return to activities

Swelling and local inflammation may be visible for a few minutes to a few hours. Discomfort may last a few minutes and is dependent on the extent of the area treated. In general, topical PRP treatment should not imply any downtime, and patients can go back to regular activities starting a few hours after treatment.

## Author's Preferred Method of Treatment

We use a RegenKit (RegenLab) that is designed to prepare Autologous Platelet Rich Plasma by centrifugation of peripheral blood in a RegenTHT vacuum tube, using a thixotropic gel for cell separation and citrate as anticoagulant. The system is simple to use, works in a closed system and produces 4 to 5 ml of Platelet Rich Plasma from 8 ml of whole blood in less than 10 minutes.

The gel in the RegenTHT tubes specifically enables the recovery of more than 95% of the platelets and isolates them from red blood cells.

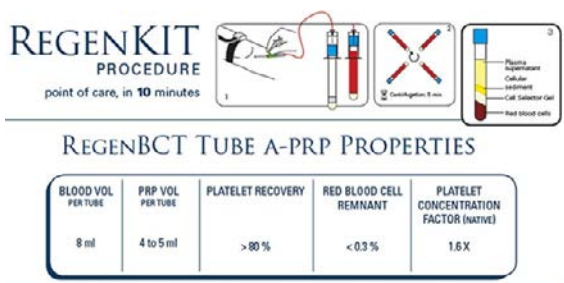


**Figure 5:** RegenKit Procedure.

Depending on the required procedure, we withdraw a variable amount of blood (8 cc for a single RegenKit) in citrate containing tubes. The blood is spun for 5 minutes at 1500 g (centrifugal force RCF) with a standard centrifuge obtaining a turbid PRP layer that is collected with a syringe and a large bore catheter paying attention not to mix it with the layers underneath.

The syringe is then constantly agitated until usage and an identifying etiquette is placed on it to make sure the sample will always match the patient.

Obtained PRP is then injected with a 30G needle in the treatment site after topical skin disinfection with alcohol 70% [13].

A cold pack is then applied and the patient is allowed to rest in supine, comfortable position for about 5 minutes. The treatment is generally repeated up to three times.

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## Chapter 9

# Autologous Fat Transfer for Face Rejuvenation

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## Abstract

The face aging is a physiological process that involves the cutis, subcutis, fascia, muscle and bone. Several different methods are available to correct these aging signs. It is only within the past 20 years that the popularity of Autologous Fat Transplantation (AFT) for facial recontouring has increased within the plastic surgery. The interest in this treatment has paralleled the development and popularity of liposuction for body contouring.

Adipose tissue has been used for volume restoration or augmentation of the face with contour irregularities, both via direct transfer and after various processing procedures. The recognition that soft tissue volume loss contributes to the aging of the face has driven the use of this procedure. At the present time AFT is the best means of restoring facial volume. It is a simple, effective and reproducible technique.

## Introduction

Aging of the face as viewed on a cellular level occurs as a result of a decrease in adipocyte cell size, function and differentiation. In addition, structural and functional changes of epidermis and dermis, redistribution of facial fat and atrophy of muscles and bone leads to the several alterations in the face as one senescence.

The clinical signs are a variable amount of wrinkling, dischromic areas, thinned and dry cutis, and volume loss in some regions and SMAS ptosis. Such processes are related to factors that are both genetic and environmental (lifestyle, diet, photoexposure, smoking habits) [1-4].

Intrinsic and extrinsic factors are the reason of these changes.

Epidermal turnover is reduced, dermal collagen is decreased and elastic material is being accumulated (intrinsic factors). Wrinkles appear preferentially on sun-exposed areas (extrinsic factors), as a prominent sign of facial aging.

Dermatoporosis is the histological aspect of aging characterized by progressive thinning of cutis, reduction of dermal papillae, elastosis or depletion of collagen and elastic fibers, and thinner of muscle fibers [5]. The loss of extracellular matrix and its major component hyaluronate, induces a damage of the skin's mechanical functions.

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Several different methods are available to correct these aging signs. Treatment are as different as infiltration of bio-revitalizing substances or filler implantation [6], or protheses [7], or chemical neurolysis [8], or tissue repositioning through lifting procedures [9]. Adipose tissue has been used for volume restoration for over a century, both via direct transfer and after various processing procedures, acutely or after cryopreservation [10]. Autologous Fat Transplantation (AFT) is widely regarded as an ideal method, addressing both biocompatibility and patient concerns [11].

Neuber [12] was the first to describe it in 1893. However, it did not attract much attention until the 1980s [10,13].

## Harvesting

The procedure consists of fat transfer via liposuction and infiltration or implantation into the desired region. It is used in reconstructive and aesthetic surgery for facial and body contouring [11,13], but also in other specialties [14,15].

Different harvesting and preparation methods have been tested to achieve greater adipocyte survival and consequently more reliable clinical outcomes.

Preparation techniques include washing with physiological solutions [16-19] and centrifugation to separate cells from debris, to minimize inflammatory responses [20,21]. Over the past 20 years, the literature has seen numerous clinical reports highlighting the benefits of autologous fat transfer for facial recontouring.

A greater understanding of how to maintain viable fat has led to modifications in technique that are believed to improve clinical results. These modifications are intended to preserve the delicate structure of adipocytes and provide a robust blood supply on which fat cells are extremely dependent [8].

There are many conflicting studies and physician experiences that exist regarding the durability and integrity of autologous fat grafts [9]. It has been suggested that variations in donor site and tissue preparation make a difference in graft take and survival [10].

## Our Technique

### Markings

**Donor sites:** Fat was collected from the abdomen (most frequently used donor site), hips, outer thighs (saddle-bags), internal knee or thigh. Preoperative markings were performed prior to anesthesia, with the subject standing.

**Face:** Comparison of a photograph of the subject at the age of 20-25 years to the latest photographs allows evaluation of the areas requiring filling (Figure 1), those merely needing

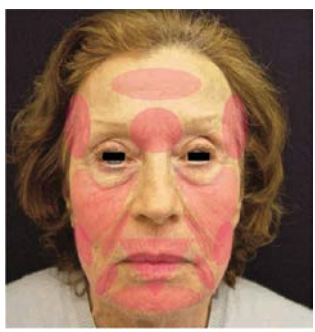

**Figure 1:** Facial marking.

rejuvenation, and those where filling would involve volume changes.

## Anesthesia

**Donor site:** A solution of 500ml saline, 25ml of 1% lidocaine, 0.5ml adrenaline, 0.25ml triamcinolone acetonide 40mg/ml and 2ml sodium bicarbonate is injected with a multi-hole infiltration cannula 1mm in diameter, whose entry point is first injected with 1% lidocaine.

The solution is slowly injected into one area and then into the adjacent one in an amount that achieves optimum vasoconstriction. It is then left in place for 45 min to obtain both anesthesia and adipocyte hydrodissection (Figure 2).

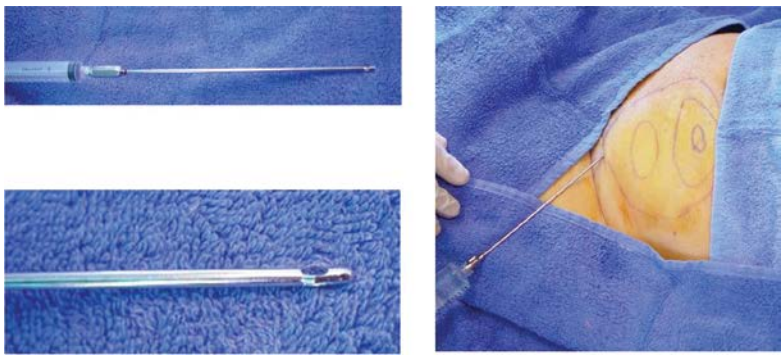

**Figure 2:** Donor site: Tumescent local anesthesia. It is then left in place for 45 min to obtain both anesthesia and adipocyte hydrodissection.

**Implant site:** Supraorbital, infraorbital and mental nerve block is obtained with 1-2cc of 2% lidocaine. In the areas not innervated by these nerves 1% lidocaine is injected subcutaneously with adrenaline, fan-wise around the areas to be treated.

No more than 2-3cc of anesthetic is injected in each hemiface to avoid excessive alteration of the oval.

**Fat harvesting:** Blunt cannulas 2mm in diameter and 10cc Luer lock syringes are used. Before collection, the syringe is filled with 1cc saline with the piston pulled back to make 2cc of void under manual regulation of the negative pressure (Figure 3).

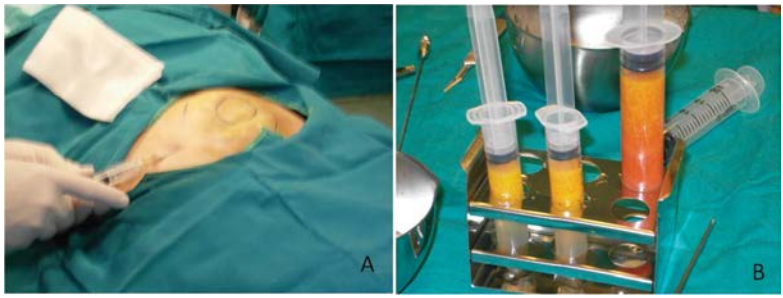


**Figure 3:** Donor site (A). Fat Harvested using 10-cc syringe aspiration (B).

**Fat purification:** After collection the adipose tissue is washed with saline, to remove all blood and cell elements (Figure 4) and left to stand; 10-12 washes yield a layer of saline and a supernatant predominantly comprised of bright yellow adipocytes and growth factors (Figure 5).

The piston is never removed from the harvesting syringes during washing, to avoid tissue exposure to air, minimizing potential oxidation.

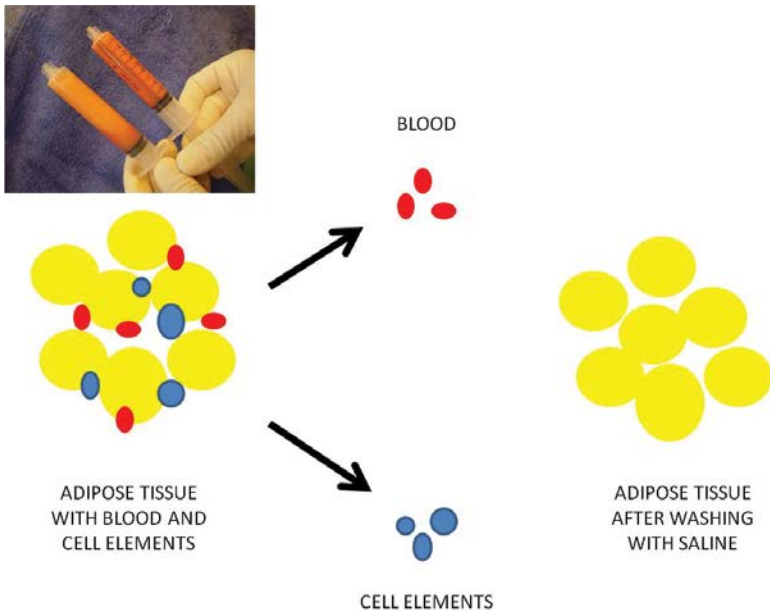


**Figure 4:** Graphic representation of fat purification's with saline.

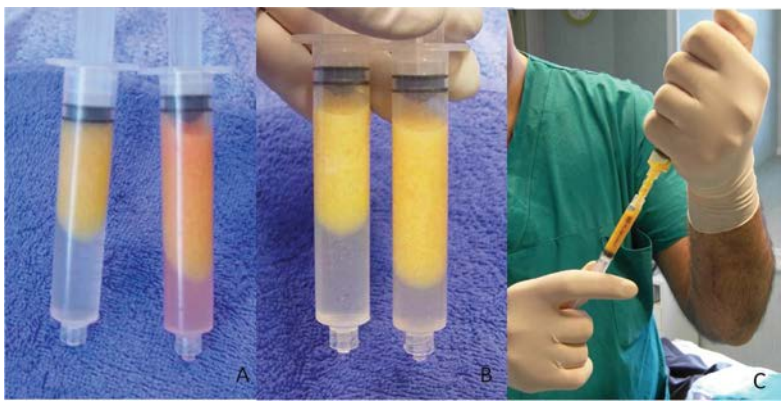


**Figure 5:** Purification of the fat.
Decanting in the harvesting syringe by placing the syringe in a vertical position (A,B). The piston is never removed from the harvesting syringes during this procedure, to avoid tissue exposure to air, minimizing potential oxidation (C).

**Fat implantation:** Small scalp incisions are made with a 18 G needle or a 11 blade to treat the temporal, supraorbital and frontal regions; at the level of the lower triangle of the malar fat pad (Figure 6); at the lateral base of the alar cartilage to treat nasolabial folds, marionette lines, and upper lip; at the corners of the mouth for upper and lower lip; and in the preauricular area for the masseter muscle and mandible regions.

The fat is implanted using a 17 G blunt-tipped Coleman cannula connected to a ratchet

gun through which doses of approximately 0.1cc fat/$cm^3$ are dispensed retrograde for each impulse. Fat is homogeneously deposited in the subcutis and above the SMAS to avoid grooves and cordons. Deposition of a single, deep subcutaneous layer provides only a rejuvenating effect, whereas multiple layers are required to achieve volume augmentation.

Careful fat deposition ensures its homogeneity. The region is gently massaged. Finally, the cannula access points are closed with steri-strip and an antibiotic cream is applied.

The method used by the authors involves fat harvesting under tumescent anesthesia and purification by washing [22,23] to preserve adipocyte viability throughout the procedure and to allow implantation under local anesthesia.

In the authors' experience the technique involving tumescent anesthesia at donor sites makes harvesting painless, with benefits that persist after the operation as analgesia (slight postoperative pain in 5.1% patients only). In addition, the vasoconstrictor action of adrenalin effectively reduces bruising (0.5% of our patients).

Recipient site pain was acceptable (slight pain in 7% of subjects) in the areas treated by local anesthesia, due to the effectiveness of analgesia through the block of the sensitive branches of the trigeminal nerve and the deep dermal and subcutaneous anesthesia provided by 2% lidocaine.

Progressive infiltration of the solution and the protracted rest phase ensure bloodless, non-traumatic tissue collection. The saline wash ensures adipocyte integrity. In addition, all steps involving adipocyte manipulation are performed using Luer lock syringes, to avoid exposure to air and the risk of oxidation.

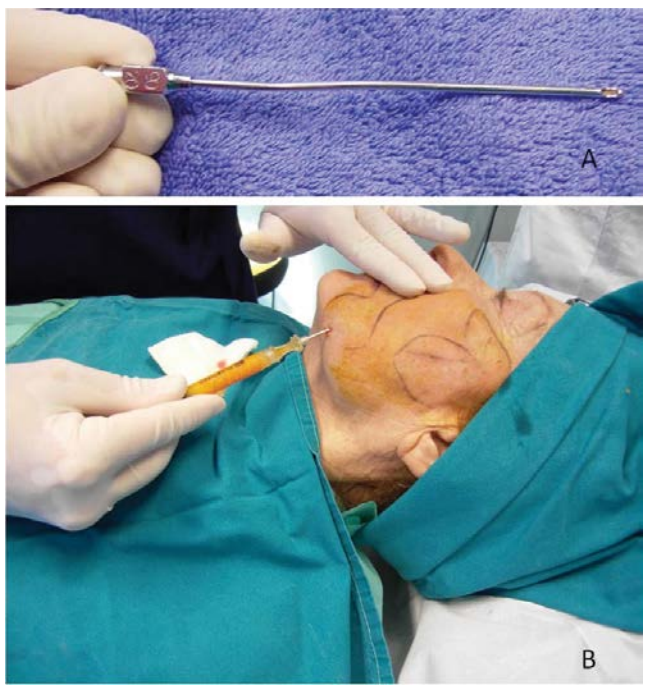


**Figure 6:** Intraoperative views of implantation, via the connection of 2mm cannula to 1-3 cc syringe luer-lok. Introduce needle into subcutaneous tissue. Inject the fat slowly drawing back the syringe.

Careful deposition of small amounts of fat in multiple layers significantly reduces the risk of fat necrosis and of subcutaneous nodules (respectively 0.9% and 4.6% in our patients). Implantation in subcutaneous regions and above the SMAS is ideal to remodel areas that have lost large amounts of fat with age.

The improved skin trophism (Figure 7) can be explained by the fact that adipose tissue deposition involves implantation of mesenchymal cells capable of differentiating, in the presence of growth factors, into fat, vessel, bone, and cartilage tissue, thus forming cells that improve dermal and subcutaneous trophism [24,25].

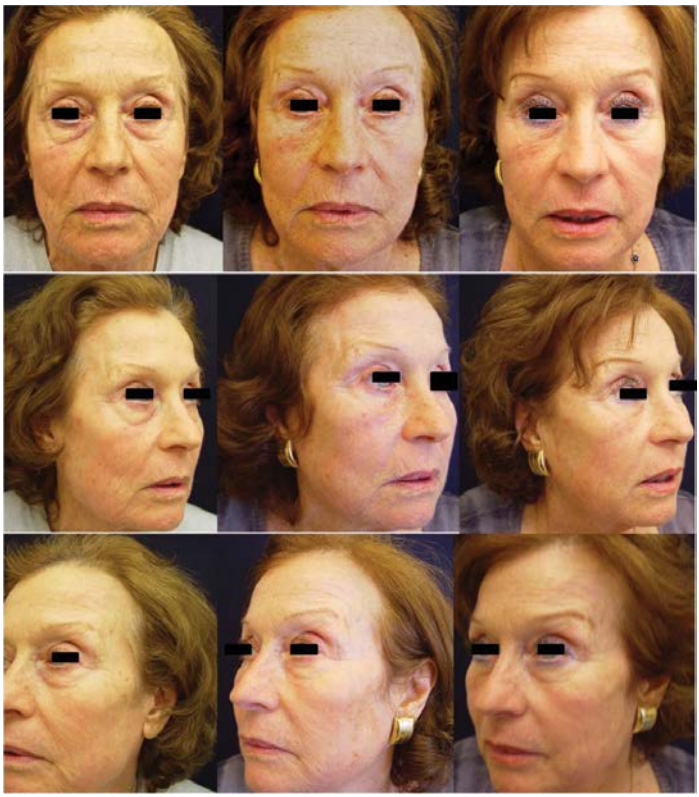

**Figure 7:** A 60-year-old woman who underwent total facial augmentation. Preoperative views (by left to right), postoperative views of AFT (in the middle) and post the second treatment in sequences.

The long-term survival of the implanted fat is due to its complete integration at the recipient site; this is achieved by bearing in mind Coleman's concept of lipostructure [26] and through careful adipocyte manipulation during collection, purification and implantation.

Preservation of adipocyte viability with our technique is ensured by tumescent anesthesia with slow, progressive injection of the anesthetic and its permanence in the donor site for about 45 min, to ensure adipocyte hydrodissection and virtually bloodless collection; fat harvesting and washing without exposure to air, thus preventing oxidative stress; saline washing according to Khater et al., [27]; and methodical fat implantation in multiple layers by dispensing doses of 0.1cc/cm$^3$ with a 17 G blunt-tipped Coleman cannula.

Despite its drawbacks, i.e. the time constraints (max 90-120min) and its contraindi-

cation in subjects who cannot bear to remain awake during any surgical procedure, the method is an effective option to treat face aging, it is reproducible, carries a low rate of complications since the autologous graft material prevents allergic reactions, and enables discharge on the same day due to lack of general anesthesia or sedation.

**Postoperative care:** No sutures are needed on implant areas, steri-strip and antibiotic cream is applied. Patients remove steri-strip after 2 days. After a further 7 days they come for a first check, and then after 3 months. Pictures are taken on both occasions.

After 3 months, the restored area is evaluated further and additional augmentation is performed (Figure 8,9).

**Figure 8:** A 36-year-old woman who underwent facial augmentation. Preoperative views (by left to right), postoperative views (in the middle) and post second AFT treatment.

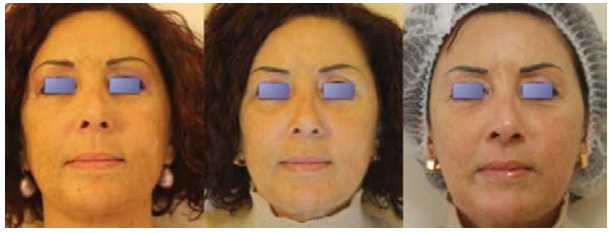

**Figure 9:** A 54 year-old woman who underwent facial AFT. Preoperative views (by left to right), postoperative views (in the middle) and post second AFT treatment.

## Discussion

Autologous fat has often been referred to as the almost ideal filler.

Nevertheless, its use remains relatively limited compared to commercial fillers. It also appears that surgically trained and oriented cosmetic practitioners are far more likely to use fat, and often as a complement to other surgical procedures such as face–neck lifts and blepharoplasty. Facial recontouring is one of the more sought after plastic surgery procedures for correction of congenital defects, traumatic injuries, or the aging face.

Numerous surgical approaches and methods have been investigated using either alloplastic materials or autologous tissue [11].

The search for an ideal soft tissue filler for use in reconstructive and plastic surgery dates back to more than a century [9]. Processed bovine collagens have been used with limited success [10]. Paraffin and silicone oil, albeit inert, highly purified, non-biodegradable and non-allergenic, have the potential for migration and/or misalignment, and secondary infections may develop as with any other product [11,12].

Hyaluronic Acid (HA), a natural component in the extracellular matrix of tissues, is found in all vertebrate animals. In the skin, hyaluronic acid provides structure and volume; the amount of HA decreases with age leading to dehydration and wrinkle formation [28]. HA is highly hydrophilic and cross-linking its polysaccharide chains slows its degradation [29,30]. Depending on the degree of cross-linking, several hyaluronic acid-based dermal filler products with varying duration of effect (6-12 months) is available [28,31]. The long-lasting effect of the HA depends on 3 factors: concentration, size, cross-linking.

It should be noted that adverse events such as swelling redness and bruising are associated with the use of these products.

Long-acting dermal fillers include calcium hydroxylapatite and injectable PLLA, and each is thought to produce their effects by inducing cellular responses that are hypothesized to result in the formation of collagen.

Common adverse events associated with the use of collagens, hyaluronic acid derivatives, calcium hydroxylapatite, or injectable PLLA include swelling, bruising, and erythema, are related to the injection procedure, and resolve within a few days. Nodules and papules, which have been reported for all the injectable devices, can appear immediately or in the weeks to months after the injection. Although most nodules/papules resolve spontaneously over several months, subcision or excision may be needed to remove visible nodules.

The guidelines for selecting AFG over available commercial fillers are not easy to set. It is difficult to justify AFG for treatment of relatively shallow nasolabial and commissural folds which can be adequately corrected with HA, or other equivalent commercial filler. AFG should be seriously considered: As cost-efficient alternative to temporary fillers; as a complement to temporary fillers, combining and layering AFG with intradermal fillers; as a possibly safer, though less predictable, alternative to permanent fillers.

Autologous fat does not cause an allergic response, has no risk of rejection, and has an effect lasting from several months to several years, although the actual duration of effect can be unpredictable. However, autologous fat requires surgical harvest and may require frequent retreatment of dynamic areas, such as the nasolabial folds and marionette lines [32-36]. In addition, adequate fat sources may be difficult to obtain in slender patients. The risk profile for AFT compares favorably to surgery, and in terms of infection, it is equal to favorable when compared to hard implants. When compared to injectable fillers, AFG has a cost advantage, especially when larger volumes are needed to treat multiple areas.

Coleman, Berman, and most other advocates of widespread use of fat grafts to increase the volume of the face (temporal forehead, brows, inferior orbital rims, malar areas, perioral areas including lips and chin, etc.), focused more on fat grafting technique, and placing the fat where it seemed to be both needed and accessible, be it supraperiosteal, sub- or perimuscular, or subcutaneous [37].

Lipostructure is a natural, long-lasting method of filling and supporting the face using intricate layering of infiltrated autologous tissue. This method allows the tissues to be

sculpted to enact three-dimensional augmentation of facial elements. Because the grafted fat becomes integrated into the host tissues, it is almost undetectable after transplantation, except by photography. To successfully use fatty tissue as such a graft, attention must be paid to the nature of fatty tissue; to the methods of harvesting, transfer, and placement; and to the preparation of the patient. Fatty tissue is a complex, delicate structure that is easily damaged by mechanical and chemical insults. Successful fat transplantation demands that every step be practiced with attention to this fragile nature of fatty tissue. Precision is an important consideration in the augmentation of millimeters of facial elements. The true volume of infiltration is difficult to judge if too much blood, lidocaine, or oil is present in the tissue being placed. Fat is living tissue that must be in close proximity to a nutritional and respiratory source to survive. Therefore, placement of small amounts of fatty tissue in multiple tunnels assumes the utmost importance in the quest for both survival of fatty tissue and an aesthetically appropriate correction. Successful, three-dimensional sculpting requires attention to patient preparation, meticulous planning, and fastidious photographic evaluation. AFT for facial soft tissue contouring is simple, inexpensive, and effective. Its ready availability, natural integration into host tissues, and potentially permanent correction make it particularly useful for this application. All patients were satisfied with the soft, natural appearance [38].

The potential applications in aesthetic and reconstructive surgeries of this new tool are profound. Lipostructure represents an important advance in plastic surgery: a safe, long-lasting method of recontouring the face with autologous tissue.

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## Chapter 10

# Nonablative Radiofrequency in the Rejuvenation of the Skin

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## Abstract

In recent years, radiofrequency has become another tool for facial rejuvenation. Radiofrequency current is formed when charged particles flow through a closed circuit. As the energy meets resistance in the tissue, heat is produced. The amount of heat will vary depending on the amount of current, the resistance levels in the targeted tissue and the characteristics of the electrodes. Initial collagen denaturation within these thermally modified deep tissues is thought to be the mechanism for immediate tissue contraction; subsequent neocollagenesis then further tightens the dermal tissue and reduces wrinkles. We use a monopolar radiofrequency from Ellman (Surgitron Dual Frequency), that combine the best characteristics of monopolar and high frequencies device. The energy and the treatment mode have been carefully adjusted so as to produce a level of heat not causing any epidermic damage or excessive pain in the area treated. Moreover, applying the tip of a 7.5mm electrode with circular movements seems to help evenly disperse the RF electricity.

RF treatments can safely be used with intense pulsed light, nonablative lasers, biorevitalizers, botulin complexes, PRP, and fillers. The majority of patients was satisfied with the procedure itself and liked the ability to return to there daily routine after leaving the office.

We determined that for in-office rejuvenation of the skin the Dual Surgitron RF device provides a measurable improvement in the majority of patients treated.

## Introduction

The gold standard treatment for the many aesthetic aspects of aging has for many years been surgery in its many forms. However, with increasing patient demand for cosmetic rejuvenation and with the strong desire and drive by patients to attain aesthetic enhancement with minimal risk and rapid recovery, there has been a strong surge inspiring the field of nonsurgical skin rejuvenation. In recent years, Radiofrequency (RF) has become another tool for facial rejuvenation [1-4].

The RF system is based on an entirely different treatment principle than the photothermal reaction created by most dermatologic lasers. Unlike a laser, which uses light energy to

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generate heat in targeted chromophores based on the theory of selective photothermolysis [5], RF technology produces an electric current that generates heat through resistance in the dermis and subcutaneous tissue.

The amount of heat will vary depending on the amount of current, the resistance levels in the targeted tissue and the characteristics of the electrodes. The amount of RF energy applied can be configured to target specific tissues. In addition, the water content of skin varies between different areas of the body, with time of the day, environmental humidity, internal hydration and the topical moisturizing agents used. Thus the flow of RF through the skin depends on multiple factors. High-impedance tissues, such as subcutaneous fat, generate greater heat and account for the deeper thermal effects of RF devices [6]. Initial collagen denaturation within these thermally modified deep tissues is thought to be the mechanism for immediate tissue contraction; subsequent neocollagenesis then further tightens the dermal tissue and reduces wrinkles.

## Radiofrequency: Which Device?

RF energy is also approved for dermatologic and general surgical procedures for electrocoagulation and haemostasis. Several radiofrequencies devices are available in the market. Depending on the construction of these electrodes, uni- or monopolar is differentiated from bipolar current application [7].

The energy field applied to tissue by the electrode configurations differs with respect to depth of penetration and side effects, while the basic cellular effects are identical. In a monopolar system a specially designed electrode emits while a usually large surface collecting electrode serves as the opposite pole. The advantage of this construction is a higher possible energy density on or in the vicinity of the emitting electrode paired with a greater depth of penetration [8]. Pain is a disadvantage. Bipolar systems usually unite both electrodes in very close proximity in one applicator. Thus, the amount of energy and its distribution in tissue can be controlled better at the cost of possible penetration depth [7,8]. RF devices have different frequencies.

The high frequency (4.0MHz) of the electric current converts the latter into a simple radio wave. This wave emitted by the active electrode naturally goes toward the passive one. Between the 2 electrodes, the organic tissue hinders the radio wave flow. At a molecular level, this resistance turns into an intracellular oscillation leading to a break in links among the water molecules contained in the organic tissue and to the related linking energy release. The thermal effect depends on the characteristics of the treated tissue conductivity. Therefore, tissues with higher impedance (i.e, the adipose ones) produce a greater heat and consequently a greater thermal effect. In this way, the energy produced by RF can develop a heat that is determined and controlled according to the superficial and deep dermis, as well as to the adipose tissue up to the muscle border. Studies indicate that tissue tightening occurs through a mechanism of immediate collagen contraction, supplemented by new collagen synthesis during a longer-term wound healing process. Ultra structural analysis of human tissues immediately after treatment revealed isolated, scattered areas of denatured collagen fibrils with increased diameter and loss of distinct borders [9].

The contraction determines a reorganization of the cutaneous tension lines in a physiological way with a reduction in cutaneous laxity caused by a tightening effect similar to a micro lifting.

## Our Experience

We use a monopolar radiofrequency from Ellman (Surgitron Dual Frequency), which combine the best characteristics of monopolar and high frequencies device. It uses a proprietary capacitive coupling method to transfer higher energy fluences through the skin

to a greater volume of dermal tissue than nonablative lasers while protecting the epidermis (Figure 1) [10].

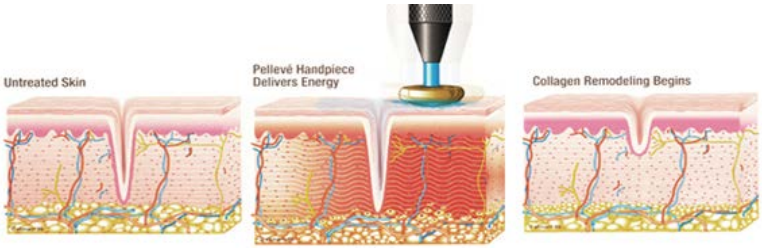


**Figure 1:** Radiofrequency waves slowly penetrate into the deep layers of skin and heat the area whilst protecting the epidermis or outer layer of skin. The heat generated causes the collagen fibres in the skin to contract and tighten, as well as stimulating the production of new collagen, helping to improve the look and feel of the treated area.

The Surgitron Dual Frequency RF heats tissue using a proprietary method of coupling monopolar RF to skin by a thin capacitive membrane that distributes RF energy over a volume of tissue beneath the membrane surface. The components of the device include:

1) An RF generator producing a 4-MHz alternating-current RF signal, the energy level of which is set by the clinician (Figure 2); and

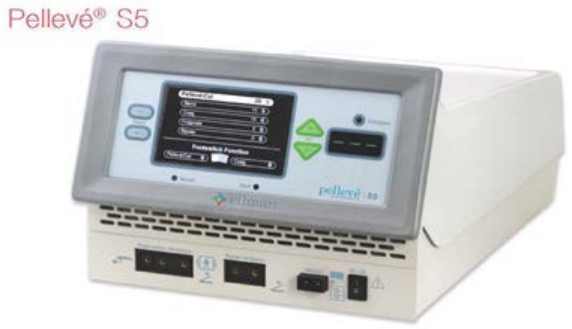


**Figure 2:** Ellman Dual Frequency - Pelleve S5.

2) A hand piece for directing the RF energy to the skin (Figure 3).


**Figure 3:** Handpieces are available in 4 sizes: 7.5mm for tightly confined areas, 10mm for less confined areas, 15mm for large open areas, 20mm for larger open areas.

The neutral plate of the apparatus is placed approximately at 15 to 20cm from the patient. Spherical hand pieces (7.5mm in diameter) are used. The application of RF energy has been carried out in ambulatory settings with no need for skin sterilization.

### Operative setting

The Surgitron 4.0 Dual RF has various operative modes. The patients were informed that for maximum benefit, the sensation should feel as if the skin is heating just to the brink of pain, but then subsiding. The settings were adjusted based on each individual patient's comfort level. Settings may vary for each anatomic region (forehead cut 20-25, cheek and other surface cut 25-30). Before start treatment we applied a restoring cream or gel to reduced side effect. The handpiece traces out spiral vectors against gravity in a diameter of approximately 1cm. Based on the patient's characteristics (subcutaneous fat distribution), a greater pressure of the handpiece was applied to cheeks and other body areas, practically absent on forehead. The handpiece action effectiveness is proportional to the pressure applied. The treatment time varies according to the area (15-20min average time). The burning sensation may vary per area as well (a more intense pain is perceived on forehead). In order to diminish the side effects (i.e, small abrasions healing in 3-4 days) it is important that the patient remain still during treatment. After treatment, a restoring cream is applied. Patients were typically able to return to work and social activities immediately after treatment.

### Contraindications

Absolute contraindications of radiofrequency therapy are implanted pacemakers or defibrillators as well as facial implants.

## Pearls

The Dual Surgitron handpiece is extremely versatile, allowing application and adjustment of the RF energy according to antigravitational factors. The smaller Dual Surgitron with a specially designed RF electrode tip (7.5mm) combined with rapid hand movement greatly reduces the deep side effects. The parameters to be taken into account for an ideal treatment are still disputable, just as the ideal level of energy needed to achieve the best result is still unknown.

The energy and the treatment mode have been carefully adjusted so as to produce a level of heat not causing any epidemic damage or excessive pain in the area treated. Moreover, applying the tip with circular movements seems to help evenly disperse the RF electricity.

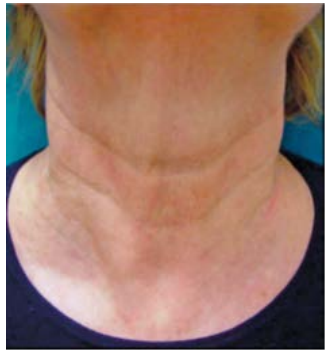

**Figure 4:** Preoperative laxity of neck.

Since anaesthetics were not used, patients could perceive any exceeding electro thermal effect, thus preventing any complications.

It is interesting to note that patients not showing a clear improvement did achieve a better skin quality and a reduction in cutaneous laxity, as can be seen by the before and after picture, even though the improvement was not very evident and therefore not perceivable by the patients themselves (Figure 4,5). For this reason, it is important to consider the patient's expectations and to explain chances for real improvement as well as the perception appraisal. Of course, an informed consent should also be obtained with comparisons of before and after pictures from the literature shown (Figure 6,7).

RF treatments can safely be used with intense pulsed light, nonablative lasers, bio revitalizers, botulin complexes, PRP, and fillers. The majority of patients was satisfied with the procedure itself and liked the ability to return to there daily routine after leaving the office. We determined that for in-office rejuvenation of the skin the Dual Surgitron RF device provides a measurable improvement in the majority of patients treated.

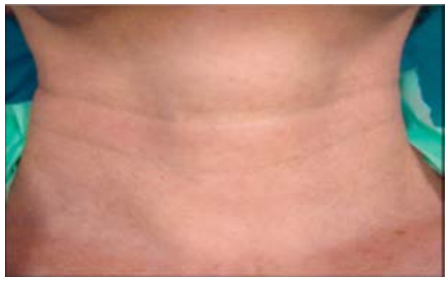

**Figure 5:** Postoperative view of neck. (three months)

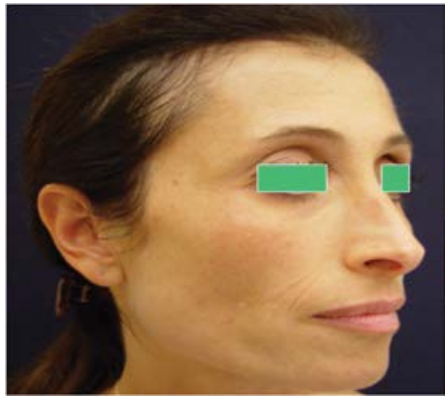

**Figure 6:** Preoperative view of face.

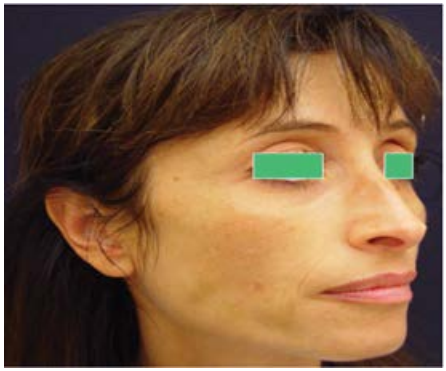

**Figure 7:** Postoperative view of face (three months).

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## Chapter 11

# Intense Pulsed Light

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## Abstract

IPL is a quite recent method that uses luminous energy. IPL photorejuvenation must be seen as soft treatment among procedures with Biomedical Lights. In this light we must not expect a too deep or invasive treatment. It is in fact a non invasive method that, despite ablative procedures, does not alter skin integrity and does not produce changes in the skin that are caused by inflammatory response and fibroblasts stimulation to produce cicatricial collagen. In ablative procedure skin is more sensitive, recovery time (down time) is extended and wounds need cures. The difference with these other technologies is the easy repeatability and slight IPL invasivity. This allows a soft therapy, but permanent in time, ease in executing, with minimum complications, low prices and especially a nonexistent downtime because there are no scabs and burns. Because of this very low invasivity, IPL photorejuvenation is considered "lunch-break lifting".

## Introduction

IPL, acronym of Intense Pulsed Light, is a technology that avails itself of a source of bright pulsed energy that, contrary to laser, is not collimated neither monochromatic neither coherent, but it has got a broad wavelength spectrum (Figure 1). The IPL, radiating a broad wavelengths spectrum, contains all the tones of colours (polychromatism), whereas the laser can generate exactly only one length of wave that is only one colour each time (monochromatism). These colours are selected by crystal filters that function as "cut off" and allow selecting the more specific wavelengths for each target that has to be treated. Therefore the system is very versatile, since modifying only the crystal filter, each pulse of light can be improved and personalized for each specific problem such as capillaries, marks, excess hairs and so on...

Therefore the IPL is a procedure able to treat various beauty flaws and several diseases (Table 1). Other essential features to add to the exceptional versatility are:

- The efficacy and the specificity, given by the ad hoc modulability for each kind of beauty flaw;
- The related security because of the scarceness and exiguity of the negative reactions

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that can occur;

- The non invasivity of the treatment, with the conservation of the skin, dearth of solutions continually and downtime almost nonexistent;

The simplicity in the application (due to the standardisation of the procedures).

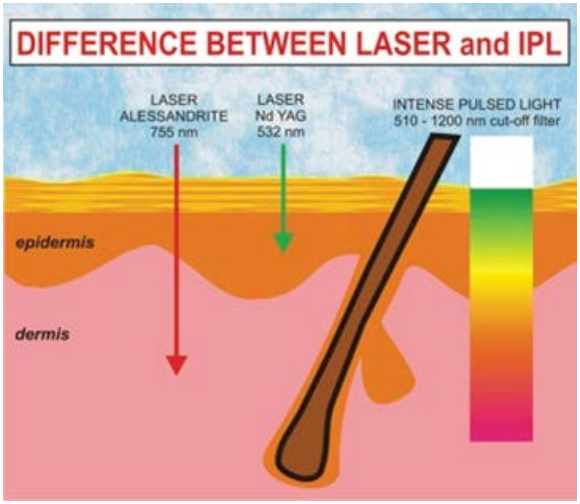


**Figure 1:** Difference between Laser and IPL.
The bright radiation, emitted by laser, is monochromatic (only one wavelength at 532 nanometre and 755 nanometre as in the example) and penetrates only at a specific depth. The biological effect is limited to that particular depth. The broad spectrum of the IPL (it is from 510 nanometre to 1200 nanometre in the example) produces on the other hand biological effects at various depths of the skin that is radiated by different emitted lengths of wave.

| Realizable treatment with the IPL | Beauty flaws – Lesions - Treatable diseases |
|---|---|
| Treatment of skin decolouration | Freckles or lentigo simplex, solar lentigo and age spot, ephelides, melasma and chloasma, cafè-au-lait macules, Becker nevus, nevus Spilus, nevus of Ota/Ito, pigmentation post inflammatory, hypermelanosis. |
| Photo rejuvenation | Degeneration of collagen, elastosis, atony, thin wrinkles, dermal atrophy. |
| Gradually permanent hair removal | Hypertrichosis, hirsutism, unwanted hairs, folliculitis, hair removal of donor areas for reconstruction (esophageal, vaginal, ureteral). |
| Treatment of vascular imperfections | Haemangioma, venous spots, telengectasia, venous lakes, senile purpuras, spider nevii, angiomas, pyogenic granulomas, small venous malformations. |
| Dermatological diseases | Rosacea, acne vulgaris, poikiloderma of Civatte, vitiligo |

The results are variable: excellent in some cases (for example in solar lentigo), negligible in others (for example in wrinkles), still under study (for example in vitiligo).

**Table 1:** The table correlates the types of treatment with the imperfections, the lesions and the treatable diseases.

The results are variable: excellent in some cases (for example in solar lentigo), negligible in others (for example in wrinkles), still under study (for example in vitiligo).

## Light Skin Interactions

The intense pulsed light technology radiates polychromatic (at more wavelengths), unstable (different range and period), not collimated (divergence of rays with consequent reduction of intensity at point of irradiation) light. The IPL wavelengths have got a range that varies from 390nanometre to 1200nanometre, including visible light and a part of infrared rays. With the system of "cut off" filters (these filters are able to select a reduced wavelengths

range) is possible to select the minimum level of length of wave that can be emitted: for example, a 640nm filter (used for hair removal) will allow the emission of rays in a range of wavelength between 641nm and 1200nm.

The electromagnetic waves, in very close contact with the cutaneous surface, withstand events of reflection, absorption, deviation or scattering and transmission (Figure 2).

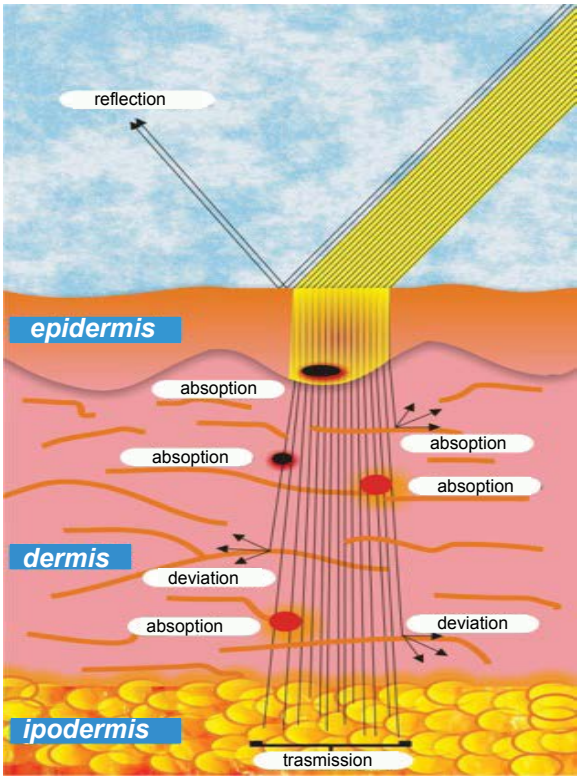


**Figure 2:** Schematic representation of the effects of bright radiations in very close contact with the skin.

- A variable quantity of light is reflected by the horny layer (about 5-10%).
- The residual quantity is absorbed by the cutaneous tissue. This absorption basically depends on the wavelength of the light and on the initial intensity. The absorption of light by the tissue determines the effect: the photons are absorbed by the target molecules or by the chromophores (optical baits) and release all the energy.
- The phenomenon of deviation (scattering) also occurs in the skin. This is due to the multitude of molecules that dwell in the derma even if it is mainly attributable to the collagen fibres. The deviation reduces the flux of energy that is destined to the target. The phenomenon of deviation decreases with the increase of the wavelength [1]. The IPL wavelength range (400-1200) is optimal because the phenomenon is scarce at these wavelengths.
- The residual light is transmitted to the subcutaneous tissues: the greater the wavelength is, the greater the penetration in depth is (because there is less dispersion of rays). The transmission also varies with the phototype [2]: the skin of light phototype transmits more than dark skin phototype (50% at 400nm and

90% at 1200nm concerning the light skin, and 40% at 400nm and 90% at 1200nm concerning the dark skin).

As mentioned above the light emitted by the IPL has got lengths of wave with a range of 400-1200 nanometre. These wavelengths are preferentially absorbed, but not exclusively, by the haemoglobin and by the melanin. The epidermis melanin will absorb both the direct light, emitted by the device, both the deflected one (scattering), irrespective of being absorbed or not by the chromophore. This has to be considered in order to avoid a real risk of heat damage to the epidermis, considering especially the types of skin with more pigmentation (according to Fitzpatrick classification this is related to high phototypes) [3-5]. According to the absorption characteristics and to the target chromophore's depth, wavelengths should be optimized in order to limit this risk. Other expedients can also be put to use in order to minimize this risk: extending the pulses and cooling down the skin before, during or after the bright pulse. The pulsed light devices are all provided with a cutaneous temperature reduction system that is in convention or contact. In addition to the intrinsic IPL temperature reduction system, several other mechanisms are used in order to minimize the epidermal damage risk, to allow high fluxes of energy, to treat all types of skin, to reduce the painful feeling by limiting the need of using local anaesthetics.

These mechanisms are the following:

- The application of a cold gel on the skin before treating the area. The transparent gel that is used is that generally used for ultrasounds (scanning gel) and it does not impede the passage of light and it facilitates the cutaneous cooling down.
- The use of cold masks to apply before and after the treatment.

## Wave Targets Emitted by IPL

The light, just emitted by IPL devices, is basically transmitted and absorbed by target molecules that are used as "optic baits" in order to determine known, regulated and predictable therapeutic effects [6]. These molecules are known as chromophores, in other words they are capable of conferring coloration to the structure where they are contained. The cutaneous chromophores can be divided in two wide categories: the endogenous chromophores (melanin, haemoglobin, collagen, water) that are molecules commonly contained in the skin, and the exogenous chromophores, that have an external origin (for example, the porphyrins generated by the *Propionibacterium Acnee* bacterium, acne vulgaris etiological agent, the exogenous pigments internalized inside the derma by voluntary processes such as professional tattoos and by involuntary processes such as post traumatic accidental tattoos).

Each chromophore has a different spectrum of absorption of luminous radiations and so it will have an optimal wavelength range for the treatment.

The IPL emitted light, radiating the skin, may determine photostimulation and phototermolitic reactions.

**Photostimulation:** The stimulation at low energy determines acceleration, through mechanisms that are not well known yet, to the tissue regeneration and to the wound healing. It is the main effect on whom the photo rejuvenation is based, conventionally considered a non-invasive and non-ablative method that allows a progressive implementation of dyscromia, both melanic both erythrosis. You can notice a fine and very fine wrinkle reduction and a pore diameter reduction after a long term of treatments.

**Phototermolitic reactions:** The luminous energy absorbed by one tissue is intended to

turn into thermal energy. This transformation is both proportional to the wavelength affinity for that tissue and proportional to the amount of received energy. The effect or wanted thermal damage is proportional to the amount of energy and therefore it is proportional to the reached temperature as well as to the exposition duration at this thermal effect. A molecular excitement is produced at scarce dose and so at low temperatures; a denaturation and a coagulation of nucleic acids and intra-extra cellular proteins is produced at larger values; a real cell explosion (photothermolysis) is produced at larger and larger values.

The selective photothermolysis concept was formulated by Anderson and Parrish in 1983 [7] and it is the main concept on whom the light application in clinical environment is based. The concept says that it is possible to use the light in order to obtain a biological effect on target structures avoiding damaging effects on surrounding tissues. The selective target chromophores demolition occurs by choosing:

- A wavelength or wavelengths range, wherein there is the major possible difference between target absorption coefficient and surrounding tissue (for example: very dark optical bait on very light tissue).
- A sufficiently high energy level that determines photothermolysis.
- A pulse duration equal or minor to Target's Thermal Relaxation Time (TRT).

Thermal Relaxation Time (TRT) is time that a structure uses to dissipate about 63% of thermal incident energy that is received energy (see next paragraph). In order to obtain pursued thermal effect without any unwanted side effects it is necessary to procure an amount of energy able to heat and denature the target chromophore in a such short time that it does not allow to devolve the same thermal energy and to cause thermal damage to the surrounding structures. Pulse duration should be shorter than target cooling-off period. When the pulse length is larger than TRT occurs as a non-specific thermal damage due to heat diffusion. Obviously the energy given to the chromophore should be sufficient to induce its denaturation and/or destruction.

## Factors that Influence Light-Tissue Interaction

The effects, mentioned in the previous paragraph, determine target or optical baits alterations in variable proportions. Such variability depends on target and luminous pulse intrinsic characteristics.

The pulse indicates the luminous emission for all its duration. It can be continuous or it can be divided in pulse portions called sub-pulses or shots. Shot sequence determines, in range of a pulse, the so called "pulse train".

**Pulse characteristics:**

- Luminous radiation time: This represents tissue exposition time to the pulse or "pulse train".
- Pulse delay: It is the interval between one pulse and the next. Sub–pulses delay is indicated with "Delay" in the pulse-train. These parameters are important for thermal relaxation time respect (TRT see next) and so important for target irradiation maximum time without any extensions and causing heat damaging diffusion to close adjacent structures.
- Target's thermal relaxation time (TRT): It depends on target chromophore dimensions, proportionally to its diameter square (small targets cool down more rapidly than big ones). Each target has got a typical dimension and so a specific TRT. However significant

differences can be highlighted within each target: hairs, for example, can be subdivided into thick, medium or fine hairs; similarly vessels can be subdivided for size. TRT can vary from little nanoseconds (tattoos) to tenth second (leg telangiectasia).

- Luminous radiation wavelength: Each cutaneous target presents its own typical absorption spectra. Choosing the appropriate wavelength range for a specific target indicates selectivity and it is essential for each treatment.
- Luminous energy is modular knowing the following parameters:
- Fluence, expresses energy density that is energy emitted per unit area and it is measured in joules per $cm^2$ (joule/$cm^2$).
- Power, is energy measurement per time unit, it is measured in watt (W).
- Irradiance, refers to power density and it is measured in watt per $cm^2$ (W/$cm^2$).
- Target localization: Target structure depth is very essential. Derma absorbs and deviates light reducing the effectiveness as it moves away from cutaneous surface. The deeper the target is the more power, emitted by IPL, shall be. Furthermore derma deviation is influenced by wavelength: the more wavelength is, the less derma deviation and absorption shall be. Anatomical localization of the area tested in treatment is important too: different anatomical areas derma presents different characteristics (for example, face presents more resistant characteristics to luminous radiations than neck and decollete). Therefore it is important to know well such characteristics in order to avoid major complications (damages to surrounding target tissue).

## Pre-Treatment and Patient Selection

The pre-treatment evaluation is made by a colloquy with the candidate and its objective exam. The purpose of this phase is to choose the candidate and individualize the right therapeutic application (for example, parameters, number of sessions, intervals between a session and others etc...) in order to improve the result and minimize complications (Table 2). The first part of the colloquy allows evaluating patients objectively (for example, phototype, qualitative and quantitative imperfection characteristics to be treated, etc.), subjectively (for example, patient expectations about the treatment, correlation between odd sensations and the presence of imperfections, etc.) and it allows subdividing into 2 categories: suitable patients and unsuitable patients.

| Pre-treatment part | Action | Aim |
|---|---|---|
| Colloquy (part 1) | - psychological assessment<br>- physical assessment | - excluding psychologically and physically unsuitable patient |
| Objective examination | - local anatomical assessment | - excluding anatomically unsuitable patient<br>- evaluating beauty flaw characteristics that must betreated |
| Colloquy (part 2) | - treatment explanation | - programming the treatment |
| Gaining informed consent | | - legal protection |

**Table 2:** Parts of pre-treatment phase.

The table shows the correct execution in order to standardise and schematize the pre-treatment phase making this phase easier but complete in every detail. Omitting or ignoring even a minor aspect, exposes the operator to any difficulties that might occur with the treatment.

Candidates may not receive the treatment because of physical reasons or psychological reasons.

**Psychological reasons** that contraindicate this treatment are the following: unrealistic expectations, exaggerated demands, peculiar characteristics (hesitant or childish personalities, anxious people or people affected by body dysmorphic disorder, people with dummy disturbs, people with familiar disapproval).

**Physical criteria** of exclusion from the treatment may be absolute or relative, temporary or permanent. This treatment has absolutely to be avoided in absolute contraindications, it may be performed but with due care in relative contraindications, it can be postponed in temporary contraindications and it can never be performed in permanent contraindications. Principal contraindications to pulsed light treatment are: pregnancy (absolute temporary contraindication), hormonal disorders (relative or permanent contraindication), epilepsy (absolute permanent contraindication), malignant cutaneous tumours (absolute permanent contraindication), recent use of alternative depilatories except for razor blades or scissors (relative temporary contraindication), photosensitising medicines or remedies (absolute temporary contraindication). Medicines with or without prescription, pharmaceutical preparations, over-the-counter medicines, must be evaluated carefully. Medical drug history must be meticulous and must include any remedy because it may cause photosensitivity reaction or it may cause phototoxic or photoallergic reactions. Various chemical substances contained in products in contact with skin may induce photosensitivity. For example, perfume ingredients, deodorants, after shave lotions, etc. In order to avoid this risk it is always better to remind patients not to apply any topical products 12 hours before the treatment. However it is always a good idea to start each session treatment by cleansing deeply in the area that must be treated. Other contraindications are herpetic reactivation (absolute temporary contraindication), active infections (absolute temporary contraindication), keloid scars (relative temporary contraindication), autoimmune diseases (relative permanent contraindication), recent exposition to luminous radiations (absolute temporary contraindication). Candidates with positive medical history for autoimmune diseases can be treated though with careful attention. In past patients with autoimmune diseases were excluded from the treatment before: high comorbid medical diseases and high severe adverse reaction risk contraindicated these patients to any luminous radiation treatment. Nowadays this position has changed because recent studies even report therapeutic effects in patients affected by vitiligo and psoriasis [8].

The local objective exam of the area that has to be treated, gives two important details (Table 3):

| Local Objective Exam | | |
|---|---|---|
| **Aims** | Verifying the existence of anatomical conditions that contraindicate the treatment | - malignant or pre-malignant skin lesions<br>- tattoos<br>- skin precarious conditions and continuous solutions<br>- active local infections |
| | Evaluating the characteristics of the imperfection to treat | - type, colour, concentration of hairs<br>- type, dimensions, vasculature of vascular imperfection<br>- origin, dimension, localization, hyperchromia depth<br>- depth, expression lines, variation, skin tonicity, skin hydration |

**Table 3:** Relevant information that may occur from objective local exam.

**Imperfection characteristics:** Imperfection evaluation must be meticulous and it must include aspects as localization, extension, number, characteristics etc. Imperfection medical history shall be done at its objective evaluation: when it has appeared, how it has evolved, it is or not the primary lesion, there are other visible lesions in other body areas, factors that worsen it or attenuate it, it has done previous treatment to eliminate it, etc.

**The existence of potential local anatomical conditions that contraindicate the IPL treatment:** Conditions, even often misunderstood, may occur in the area to be treated and

they contraindicate the IPL treatment. These conditions are: pre-malignant and malignant lesions, tattoos, continuous solutions and skin precarious conditions, active local infections (acne excluded because it is one of the main IPL uses).

In the second part of the colloquy, patients shall comprehend the principal characteristics of their imperfection type that is medical diagnosis, etiopathogenesis, how to avoid or prevent relapse and how to magnify or stabilize the result. After giving any type of information to patients of their own imperfection, treatment will be examined in details: IPL action mechanism, alternative treatments, treatment duration (purely empiric and based on characteristics, imperfection type, individual reaction, with susceptibility of variations according to session progression), session characteristics (pain, etc.) long term result (variable according to imperfection characteristic and imperfection type), information about the pre–treatment and post-treatment phase (for example, not to expose to the sun for 4-5 days, to indicate potential adverse events such as shaving your body before being treated of permanent hair removal), side effects and complications, treatment costs, combination of other treatments, potential treatments to associate to the IPL.

Individual forms and informed legal consent shall be completed at the end of the pre-treatment phase, after having received the positive consent by candidates to make this treatment. Such forms are very important because they allow to set the treatment by decreasing potential mistakes, optimizing each session in order to improve final results, obtaining the highest grade of collaboration from patients (necessary measures and prohibitions in the pre-treatment phase and post-treatment phase). Individual forms are: information form about the treatment, data acquisition form, operating form.

**Information form about the treatment:** This form, completed and handed to patients, provides a quick but essential situation about the behaviour that should be adopted before and after treatment sessions. Patients will always be aware of medical recommendations. Specific parts and individual parts for each patient and each imperfection may be added to generalize information form.

**Data acquisition form:** This form must report patient biographical data, relevant anamnestic information, patient details (skin type, phototype, etc.) and imperfections details (hair type, imperfections characteristics, area to be treated, etc.). It is advisable to be as much detailed and specific as possible: spending more time in the compilation, implies a bigger simplicity in executing treatment sessions and it implies a small complications incidence.

**To be treated imperfection/lesion picture** with eventual release form for the publication.

**Operating form:** Operating form is an indispensable document for the doctor who shall execute the IPL treatment (Table 4). The form is initially completed in the biographical data page during the pre-treatment visit. Afterward, at each session, technical information shall be reported: the session data and the session number, the used power, the number of phases completed on the skin alteration that has to be treated, the used parameters (spot length and interval between these), thermic reaction at the end of the session, pain reaction felt by patients, result that is obtained during the session (estimated at next session).

The doctor, before executing the first session or the next ones, shall always consult the operating form in order to evaluate the treatment course, shall avoid the beginning or adverse events occurring (they must occur only in rare cases), shall put all those devices that will be useful to optimize the treatment into practice (change of parameters, power increase and so on).

**OPERATING FORM**

Date ..... Name/surname .....

Treated area .....

| Date | Session | Power | Nr of passes | Parameters | Thermal reaction (for example redness, soft rinds,bubble, for……..days) | Pain reaction (mild-moderate-intense-severe) | Result |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
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Notes: .....

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Attention: the level of satisfaction of patients should be evaluated after each session

**Table 4:** operating form example (model). The use of this form is essential, especially for treatments made in more sessions.

## The Treatment

The device gets started in order to control its functionality. Cooling water level shall be evaluated during this procedure as well integrity and cleanness of all components (especially filter and handpiece). After the check up of the device it is necessary to select rightly the handpiece and the parameters for the forthcoming session. The handpieces (Figure 3) are different for spot dimension and so for area spaciousness that can treat. In order to treat wide areas it will be useful to adopt handpieces with a big spot so that the session is minimized (for example back hair removal). On the other hand it will be imperative to adopt handpieces with a small spot to treat small areas (for example whisker hair removal) or irregular areas (for ex. nose treatments) or small imperfections (for example small angioma) in order to have a bigger control on the emission of luminous radiation. Cut off filters (Figure 4) are different for wavelength range selection that they manage to filter and so for treatable disease (Table 5). It is linked one or more treatable disease for each filter. Some latest generation of devices have got a handpiece for each cut-off filter; in this case it will be necessary to adopt the right handpiece with the right filter for the disease that has to be treated.

**Figure 3:** Handpieces of the same device with different spot dimensions. Each handpiece is indicated for different situations.

**Figure 4**: cut-off filters.

Some devices present different cut-off filters, to apply on the same handpiece, modifying wavelength range emitted and the selectivity. Other devices have got different handpieces with different cut-off filters which mean each one has got a different wavelength range emitted.

**Cut-off filters**

| Filter range | Indicated treatment |
|---|---|
| 690-1200nm | photo-hair removal blonde/brown hair |
| 640-1200nm | photo-hair removal dark hair |
| 560-1200nm | photorejuvenation |
| 510-1200nm | skin spots and vascular treatment |
| 430-1200nm | acne treatment |

**Table 5:** Examples of cut-off filters that are specific for a specific device.

The table shows the correlation between cut-off filter and imperfection type. The choice of the right filter within a treatment improves the outcome in terms of result and complications reduction.

The treatment comes before test execution, an act of great caution, especially in particular patients (dark phototypes IV-VI Fitzpatrick, patients who present relative contraindications). Despite of selection and evaluation of patient suitability to execute IPL treatments, made in the pre-treatment consultation, it actually remains to verify the normal responsiveness of patients to IPL treatment. This test can be made during the pre-treatment consultation or during the first session (1 hour earlier). The device must be regulated with patient's parameters (just as they would be treated), then one single spot is done directly on the to-be-treated area. This test has the purpose of evaluating potential adverse effects and complications not the result. This test helps to avoid professional mistakes. When complications occur, two different attitudes can be adopted:

- If complications are relative, parameters must be correct (for example, reduce the fluence, increase the pulse delay etc.) and a second test must be done in a different area.
- If complications are more serious, it is advised not to treat patient.

When the test result is negative which means there is no complication, patients can be treated. The choice of application of topical anesthesia (ointments, creams, anaesthetic gel) is based on operator discretion or judgment. Pain perception is very variable from one person to another and it is increased progressively with the increase of the fluence and wavelength.

Before starting to treat patients it is necessary to complete a right setting of parameters to use (Figure 5). These parameters should consider imperfection types (for example hair thickness and hair colour, vessel location and dimension) and patient's characteristics (for example patient's phototype, sensitivity to pain, and results of previous sessions). Patients operating form will be useful at this point to evaluate the parameters of the previous treatment and the factors that can influence on the modification of these (perceived pain, adverse reactions, obtained result, etc.). Power cooling level must always be set at maximum cooling level.


**Figure 5:** IPL device control panel.

Devices often have advanced programs with memory functions, pre-set programs, etc. observing indications imparted by manufacturer (reference parameters, settings in the pulse train, cut-off filters, etc.) is very appropriate at the beginning, during the execution of the first treatments.

Parameters are normally given in tables by devices producers. It exists a wide variability among different devices, especially for what concerns the fluence and the pulse train parameters (Figure 6). So it's dangerous to use generic parameters or other devices parameters. It is always advised to operate with caution. Observing device reference parameters, which are advised by the producer initially, is very cautious; afterward it is possible to modify-personalize parameters on the same patient having more experience and passing session by session.


**Figure 6:** Example of video screen for the pulse train settings.

Up parameters correspond to (i) 7.0ms - first and third shot, (ii) 9.0ms - second shot, (iii) 19ms - first and third delay (or pulse delay) and (iv) 15ms - second delay.

After setting parameters it is time to treat patients:

- Placing patients on the table in a comfortable position and optimal to treat the area.
- Cleansing skin. The area that has to be treated must be cleaned with wet gauze soaked in saline solution or make up remover cream. It is compulsory to pay attention to remove make up from the face. Make-up can interfere with light transmission and absorption.
- Evaluating skin in the areas to be treated. This must be integral, without continuous solutions and irritative processes (except acne in an active phase). Long hairs may be cut off with razor blade, razor or scissors.
- Moles and tattoos shall be evaluated and memorized in their position. These ones, in fact, shall not be irradiated during the treatment. Before applying electrical conductor gel, it is normally advisable to cover them by colouring them with eyeliner

of white colour. Such operation will make moles and tattoos totally refractory to rays absorption, emitted during the spot.

- Applying a layer of cool electrical conductor gel. Even if it will slightly reduce the fluence, this gel will considerably reduce the risk of post-treatment adverse reactions and it will ease pain. Gel shall not be used in local hyperchromia treatment and vascular imperfecions.
- Putting protective spectacles on patients and remind patients to keep eyes closed until new disposition. Operator shall put protective spectacles too. Protective spectacles must be put on by patients and medical staff for all the treatment period.
- Positioning the handpiece in direct contact to skin. If gel is applied, the handpiece shall be lightly separated from skin, in order to make gel interpose between the handpiece and skin, thus creating a double interface handpiece-gel and gel-skin. Cooling well the area below the spot (about 5 seconds) before executing the spot. This will reduce pain feeling and the incidence of after-treatment reactions. Sometimes, especially in long treatments, it is advisable to touch the crystal of the handpiece in order to evaluate the cooling capacity; during treatments in which several spots are executed (or example full face hair removal), the cooling capacity of the device decreases. In this case it is advisable to await few minutes in order to guarantee the restore of the cooling capacity of the handpiece.
- Executing the spot. The first session of the session's cycle always start with low fluence, setting parameters at inferior limit of the reference parameters form. This first session will be useful to comprehend patient's cutaneous reactivity to this treatment and avoid unpleasant adverse effects. At each session it is always good practice to start with few spots of reduced fluence (less than 20 per cent), in order to get patients used to painful feeling that is fleeting but intense. Adjusting the power in the passage of an anatomic district to another (for example in the passage from face to neck it is necessary to reduce the power).
- Cooling well the area below the handpiece after executing the spot. When it comes to devices with water-cooling handpieces it will be sufficient to maintain for a few seconds the handpiece in the same position of the spot just executed.

The treatment must be executed in a systematic way, according to specific indications for each procedure for several imperfections: executing more passages possibly crossed in permanent hair removal and in acne, executing one single spot or double spot in hyperchromias and in vascular imperfections. It is very important to create mentally a schema of the treatment to be executed and execute that schema literally in order to treat in a homogenous way each single part of the area to be treated.

## The Post-Treatment Phase

It is always advisable to apply in the imminent post-treatment phase, after cooling derma, lenitive creams composed with zinc oxide or Aloe. During the twelve hours after the treatment it is advisable to avoid conditions that may increase cutaneous temperature: saunas, hot showers, excessive physical stress, etc. During the following days it is strongly encouraged for patients to avoid intense exposure to the sun or tanning saloons in addition to photosensitising medicines. In general we recommend 4 days but this may vary depending on skin phototype, kind of lesion, number of session, etc. Furthermore patients shall literally execute the house topical treatment (for example using whitening creams or hydrating creams, etc.). Check-ups, in case of normal after–treatment course, are performed by 24 hours and one week; it may be sufficient verbal consultation, whereas after 3-4 weeks it is necessary a visual evaluation. The first two check-ups has the purpose of monitoring the

insurgence of complications, on the other hand third check-up evaluates both complications both session results. Interval between treatments is initially decided according to imperfections and phototype, afterward according to patient's response. If complications occurred, interval shall be longer. Relatively short times for session's execution and the quick recovery have made the IPL treatment to be considered by American people a "lunch-break lifting".

## Adverse Events and Complications

As in all medical-aesthetic treatments may have complications, it may happen in IPL treatments as well. Many of these reactions may be prevented, avoided and minimized by having device, knowing therapy basics and knowing their treatment strategies (Table 6). Adverse events correlated to IPL treatment can be divided in major and minor events. Each group presents frequent adverse events and infrequent adverse events. It also presents premature and tardive adverse events. From a clinical viewpoint adverse events can hesitate from an excessive post-treatment reaction (upper-grade burn, skin damage caused by thermal injury) or can be independent from this reaction (Table 7).

| CAUSES | Predisposing factor | Treatment phase | Critical point |
|---|---|---|---|
| **Operator mistakes** | - insufficient experience<br>- formation lack<br>- excessive procedure competence | - Pre-treatment<br>- Treatment<br><br>- Post-treatment | lacking selection<br>wrong parametres<br>excessive fluency<br>wrong management/therapy |
| **Depending by patients** | - anomalous skin reactivity<br>- insufficient patients compliance in pre and post treatment phase | - Pre-treatment<br><br>- Treatment<br><br>- Post-treatment | compliance lack (patients do not accomplish assigned dispositions)<br><br>skin iperactivity<br>compliance lack (patients do not accomplish assigned dispositions) |

**Table 6:** Evaluation during all treatment phases of critical points and potential causes for adverse events onset.

| Adverse Event | Incidence | Graveness | Sorgence | Heat Damage |
|---|---|---|---|---|
| erythema and edema | frequent (the more fr.) | **minor** | premature (immediately after treatment) | yes |
| vesicles, blister | infrequent | **minor** | premature (immediately after treatment) | yes |
| purpura | rare | **minor** | premature (immediately after treatment) | no |
| haematoma | infrequent (in vascular tr.) | **minor** | premature (immediately after treatment) | no |
| scabs | frequente | **minor** | premature | yes |
| infections | infrequent | **minor** | premature | no |
| zebra apperarance | infrequent | **minor** | premature | yes |
| transitory hyper-pigmentation | frequent | **minor** | tardive | yes |
| temporary hypochromatic variations | infrequent | **minor** | tardive | yes /no |
| temporary hair discoloration | rare | **minor** | tardive | no |
| permanent pigmentation variations | infrequent | **major** | tardive | yes /no |
| stimulation to hair growth | infrequent | **major** | tardive | no |
| leukotrichia | infrequent | **major** | tardive | no |
| uveitis and iritis | infrequent | **major** | tardive | no |
| scars | infrequent | **major** | tardive | yes /no |

**Table 7:** Adverse event's characteristics that may occur after IPL treatment.

Adverse events are the following:

**Erythema and edema:** They represent heat damage sign of minor entity (first or second degree superficial burns); it appears in a few minutes after treatment and it remains for a variable time period (minutes, hours). It is the most frequent reaction type after IPL treatment (Figure 7). They can be of all grades (mild, medium or severe). They are considered adverse events if they remain for more than 48 hours (Figure 8), otherwise they have to be considered as a normal cutaneous response to IPL radiation (treatment efficacy index).

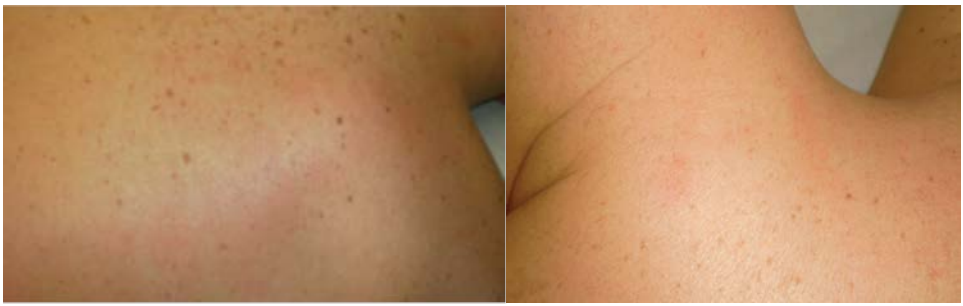

**Figure 7:** Mild erythematous reaction after treatment.

A reaction of such entity disappears in 12 hours. It is not an adverse event, it can be considered on the other hand index of right treatment execution.

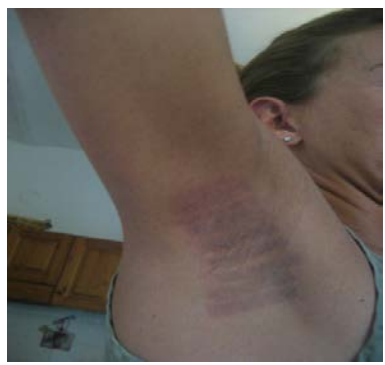

**Figure 8:** Severe burn erythema caused by use of an excessive fluence for axillary hair removal treatment with IPL.

This photo has been taken 24 hours after treatment. Different coloration areas are visible: red-vinasse externally and brown-dark brown centrally. Brown-dark brown zones have been put to deeper fluence due to the fact that they are central and they are evolving in scabs. Such lesion may give permanent results (scars, permanent spots) if not treated properly.

**Blisters:** They are the consequence of medium-severe degree heat damage (severe second degree burn). Blisters preserve however infections above as long as they do not blow up. After one treatment, blister is a type of initial lesion that can restore ad integrum restitution even though with a long hypochromia phase. For this reason it is necessary for a careful medicinal management.

**Purpura and haematoma:** They can last few days or up to 14 days. Rarely occurred, they take place immediately after treatment and prevailingly during vascular lesions treatments.

**Scabs, infections, scars:** These are secondary lesions caused by heat.

**Zebra appearance:** It is due to heat lesions imputable to 2 potential mechanisms: scarce homogeneity in the spot distribution on the area to be treated, when spots overlap zones are formed (damaged zones) and not treated zones (intact zones); the insufficient capacity of the system and handpiece to return at cooling temperatures between one spot and another (one spot, at limit fluences for skin types, is rightly cooled whereas the next one is not). This comes usually in hair removal treatments. Damaged areas are hypochromic with dimensions and geometric figures that trace totally or partially the used handpiece imprint (Figure 9).

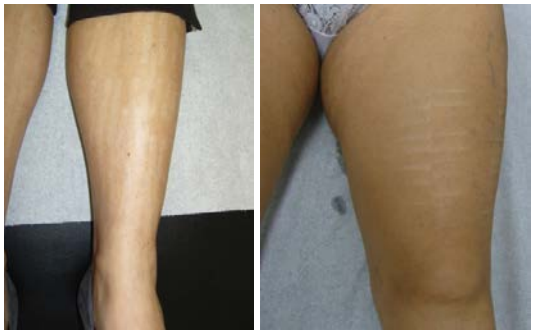

**Figure 9:** Zebra appearance.
Lighter areas are due to partial crystal overlap during spots' systematic progression in parallel. For this reason it is always preferable to use multiple crossed technique. This technique schedules crystal disposition in a direction with abreast parallel progression and after that it schedules a further passage in the treated area in orthogonal direction: this assures a distribution homogeneity of luminous radiation.

They are transitory hypochromes given by a melanocytic "resentment" of excessive heating, and it is one of the first warnings of energetic overdosage (so it is right to proceed carefully).

**Transitory hyper-pigmentation:** Local skin darkening may occur after IPL treatment. It is usually transitory and it disappears in few months. Patients with dark phototype are more disposed to this reaction. This kind of complication is often associated to a bad management of post-treatment phase. Patients who exposure to sunlight prematurely or who often go to tanning salons are highly at risk. It is a very frequent occurrence in darker phototypes .

**Temporary hypo-chromatic variations:** Hypo-pigmentation is due to burns that have caused a temporary or permanent damage to melanocytes. Damage severity is obviously correlated to the grade of the excessive fluence when compared to TRT and therapeutic window established by TRT. Temporary post-treatment hypo-pigmentation seems to be correlated to melanogenesis suppression and it is not due to melanocytes destruction [9]. This may justify the fact that such phenomenon is temporary. In case of permanent damage, permanent hypo-pigmentation may occur to melanocytes.

**Permanent pigmentation variations:** Variations can be hypo or hyperchromic (hyperchromic variations are more frequent). Hyperpigmentation is more frequently caused by vessels destruction and consequently by hemosiderin deposit in the derma. Patients with dark skin are more frequently disposed to cutaneous pigmentation variations. Their melanocytes are probably more reactive to warm stimulation.

**Stimulation to hair growth:** According to some recent studies, about 10% of patients subjected to permanent hair removal treatment with IPL or laser, develops this paradox effect [10,11]. This phenomenon is highly observed in areas with thin hairs such as face.

New grown hair will be thicker and darker. Hair growth, or new hairs, is linked to bulge activation phase of those follicles that are not in active phase during the treatment. Some new hairs may grow over time, especially in young patients.

Adverse event'Ss incidence, especially graver ones, is highly reduced with modern IPL devices. However it is always advisable to be careful and recognize those patients who are predisposed to develop those events. Cooling method and avoiding the exposure to sunlight before and after the treatment are fundamental to minimize risks of adverse effects and damages. Avoiding adverse events means to comply all those warnings that have been discussed in previous paragraphs: during each treatment phase it is compulsory to pay great attention for each operation that is executed (Table 8). IPL treatment must not have inherent doctor and patients' hope that there are not permanent complications: it is not a challenge on how much you push yourself beyond the limits. You must seek the absence of undesired side effects and you must set security parameters. When adverse events occur it is highly recommended to increase time interval between treatments in order to have a complete cutaneous recovery. There are no clear recommendations in literature about treatment resumption or frequency. As a basic principle it is advisable to postpone the treatment some weeks later (2-6 weeks later according to complications entity) and however not before the complete recovery. Fluence and interval between pulses must be set so that they reduce energy in treating skin.

| Treatment Phases | | |
|---|---|---|
| **Pre-treatment** | to prevent | excluding not eligible patients<br>identifying treatable patients but with potential complications |
| **Treatment** | to prevent | executing test<br>executing each step correctly<br>setting right parameters and fluence<br>cooling well before, during and after |
| **Post-treatment** | to prevent<br>treating<br>minimize complication's entity and course | teaching right advices<br>prescribing right post treatment therapy<br>identifying immediately complications and treating them quickly |

**Table 8:** Each treatment phase has got an important role in preventing adverse events. In this table main actions, on which to pay great attention, are described for each phase.

## Photorejuvenation

Skin aging is a physiopathological process that is the result of several factors, extrinsic or intrinsic. The methods of presentation are varied and characterized by the concomitant presence of pigmented lesions (mottled pigmentation, hyperpigmentation macules, etc.), vascular lesions (telangiectasias, etc.), wrinkled skin and dry skin. The term photorejuvenation describes the simultaneous improvement of various skin changes associated with aging through the use of light radiation (Table 9). The process of non-ablative photorejuvenation with IPL aims to reduce quantitative and qualitative extent of these injuries through the heating mechanisms, regression dermatological and endothelial disruption. By now, many methods are used for the improvement of skin that is damaged by the photoaging process. The quality of aged skin can be improved by ablative treatments and not, the difference between these two methods is that the first cut off skin integrity with solutions continuously, while the second does not affect the integrity of the skin [12,13]. This entails a recovery time incomparably faster in the non-ablative treatments. The Intense Pulsed Light (IPL) is a relatively recent technology, non-ablative, used for skin rejuvenation. Photorejuvenation with IPL treatment should be viewed as soft procedure between biomedical lights. In this perspective, we should not expect a too deep or too invasive change. For the treatment

of wrinkles and/or skin blemishes, important vascular and/or inveterate stains, the non-specificity of light IPL makes it advisable to rely more on targeted wavelengths as 1540nm or 1064nm, 532nm, 585nm laser or q-switched, erbium, $CO_2$. The difference with these other technologies lies in easy repeatability and slight invasiveness of the IPL. This therapy allows a slight, but constant in time, reduced costs, compared to laser treatments and especially a non-existent down-time without any scabs and burns. A hyperchromic macula, treated with $CO_2$ laser, for example, takes months before healing, with the risk that, in the meantime, patients undergo unprotected exposures to sunlight with restimulation of melanocytic component. The IPL progresses in clearing of the injury (Figures 10,11), as it is always constant and repeated the procedure. Because of this very low invasiveness, that is a slight redness that subsides within a few minutes/hours, because of the slight evidence of the darkening of pigmented lesions, skin rejuvenation with IPL is considered the "Lifting of the lunch break." Non-invasive methods for rejuvenation, such as IPL, need to compete with the laser-resurfacing, chemical peels and dermabrasion. Ablative procedures affect the epidermis and produce changes in the derma followed by an inflammatory response that stimulates fibroblasts to produce cicatricial collagen. In these situations, the skin is more sensitive, the healing time (downtime) is extended and the wounds need cures [14]. The main advantages skin rejuvenation with IPL is minimal downtime, minimal interference with lifestyle, the speed and ease of execution of the treatment, minimal complications and long-term improvement.

| Hyperchromias | Vascular Skin Lesions |
|---|---|
| Lentigo simplex | Teleangectasias |
| Solar lentigo and senile | Venous lakes |
| Ephelides | Senile Purpura |
| Cafè-au-lait macules | Hemangiomas |
| Melasma e chloasma | Cherry angiomas |
| Baker nevus | Wine stains (port-wine stains) |
| Nevo spilus | Rosacea |
| Nevus of Ota/Ito | Spider angiomas |
| Post-inflammatory pigmentation | Piogenic granuloma |
| Hypermelanosis | Venous malformations |
| | Venous lakes |

**Table 9:** The cutaneous hyperchromias and vascular lesions can be treated with IPL.

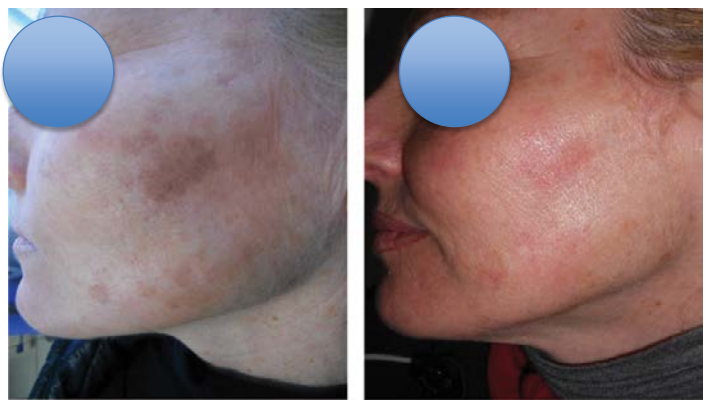

**Figure 10:** Solar lentigo senile in 55 years old woman.

Although the patient does not present wrinkles, skin laxity, or other signs of aging, the presence of numerous and large hyperchromic macules masks the value (right). Result after 3 sessions (left).

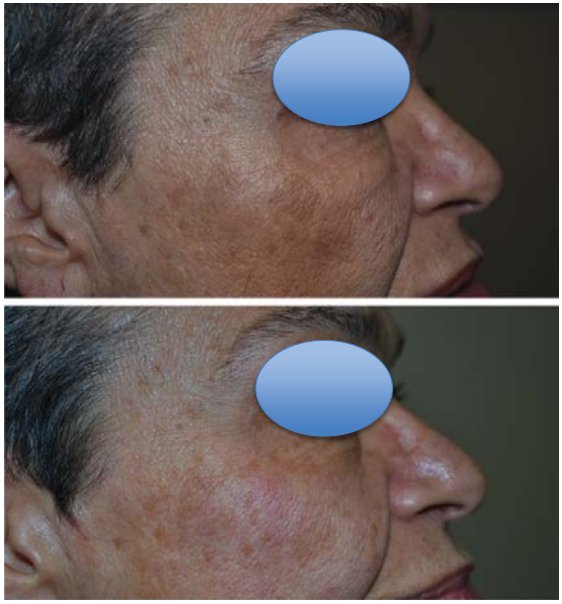

**Figure 11:** Subject with numerous lesions hyperpigmentation in the face that is subjected to the treatment of photorejuvenation. The two photos show the quantitative and qualitative reduction of dischromic imperfections.

**Pre treatment:** The goal of rejuvenation in general is a reduction of discoloration, vascular blemishes and improve skin texture. The physician should explain well to patients the difference between the expected results with IPL technology and those results with other ablative technologies ($CO_2$ laser, deep chemical peels, etc.). The fact that vascular and pigmentation improvements will be noticed after several months and the fact that fine wrinkles and skin texture will improve almost a year after, it should be stressed during the consultation.

**Treatment:** The rejuvenation treatments mainly concern face, neck, chest, although we always advise patients to treat the back of the hands for the great improvement that is generally achieved (especially in the presence of keratotic lesions and hyperpigmentation). The treated area is covered initially with a single, systematic, grating passage in all the areas to be treated. In this first step the aim is to improve skin texture and stimulate dermo-epidermal regeneration. The second step will be performed, at greater fluence, solely on the focal lesions (spots, spider veins, etc.), with a single spot technique, according to the specific instructions for the type of target lesion. Alternatively, vascular lesions can also be treated in a different session to improve the results. The footprint is always placed perpendicularly to the skin. In areas with hyperpigmentation it must be exerted a slight pressure despite the areas with a predominance of vascular abnormalities where no pressure should be exerted. In this way, the blood vessels do not empty and the treatment is more effective. Near hairy regions, such as the eyebrows or scalp, these must be covered with white gauze and the IPL footprint must be placed 2-3mm from the edge, to prevent unintentional hair removal. The execution of the entire unit cosmetic treatment is recommended in photorejuvenation. The bleaching of the vessels, associated with an urticarial reaction type, or the slight darkening of pigmented lesions, immediately after treatment, are indicators of good response to treatment. The timing of the session varies depending on the anatomical area, from a few minutes to more than 30 minutes for face, neck and chest. Ice packs are always used at the end of treatment in order to reduce edema and the burning sensation. Almost all patients

are able to resume normal activities after the procedure. Some patients experience a burning sensation which disappears in a few minutes. The erythema and edema are present in the majority of patients and will clear up in a few hours up to 2-3 days. Pigmented lesions darken for the next 7-8 days, giving rise to thin flat , non-palpable scabs. This phenomenon is not to be considered as a complication, unless it continues for a longer period.

**Protocol:** The intervals of the sessions for skin rejuvenation are variable from 2 weeks [15,16,17] to 8 weeks [18]. The majority of physicians perform treatments a month away. In our practice we perform a treatment every month for a total of 5-6 sessions, even if this interval is arbitrary. For people with post-treatment side effects or increased skin sensitivity, we extend the interval between treatments. The cycle of sessions must be repeated each 1-2 years, depending on the characteristics and type of injury, in order to maintain a stable result. In the case it is not detected any improvement of vascular and pigmentary lesions or it is detected a minimal improvement, the fluence should be increased. Usually an increase in the fluence of 5-10% in the next session, increases the effectiveness of the treatment while preserving security. Obviously, in order to increase treatment, there should not be any complications. The skin is not a uniform structure and lesions are present at different levels of the derma. For this reason it is preferable to alternate cut filters (cut-off) rather than a single range of different wavelengths. The regression of results is a normal process which occurs after every aesthetic procedure. The regression of results due to IPL usually occurs from one to a few years after treatment. Maintenance treatments, that should be performed each year, are recommended to continue to enjoy the positive effects [19] and prevent the new onset or prevent the accumulation of lesions which are typical of senescence.

In our experience, the highest patients satisfaction occurs for pigmented lesions (Figures 12,13) and vascular (Figures 14,15) as part of photodamaged skin. Shorter wavelengths are better for the treatment of these lesions; longer wavelengths penetrate deeper and are better for reducing wrinkles and improving the texture [19]. In our experience we have not seen significant improvement in skin texture after the IPL treatment. During the consultation we stsrongly emphasize that the significant improvement in skin texture is not obtained with this method. If patients understand this, the level of satisfaction will be high.

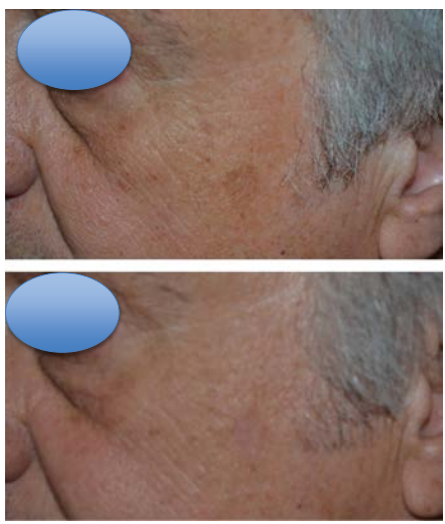

**Figure 12:** Subject with age spots, fine wrinkles. The subject has undergone photorejuvenation treatment. Result after treatment with IPL.

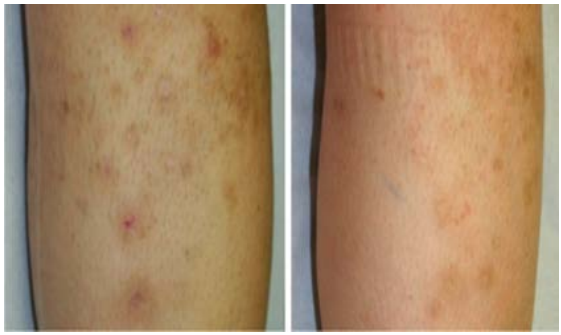

**Figure 13:** post inflammatory hyperpigmentation folliculitis (left). Monthly sessions with IPL causes a progressive regression of the hyperchromic lesions (right, after 3 sessions).

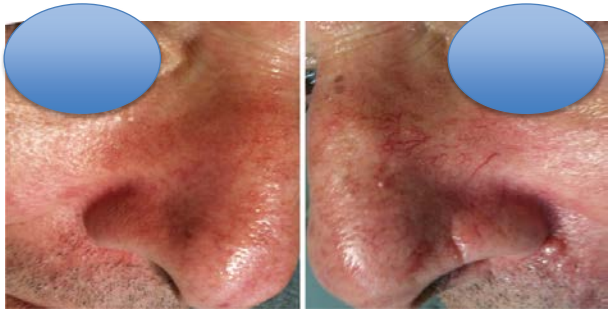

**Figure 14:** Teleangectasias of the nasal pyramid.

The right side of the nose is treated with 5 sessions of IPL (a session each 3 weeks). The left side of the nose is not yet treated.

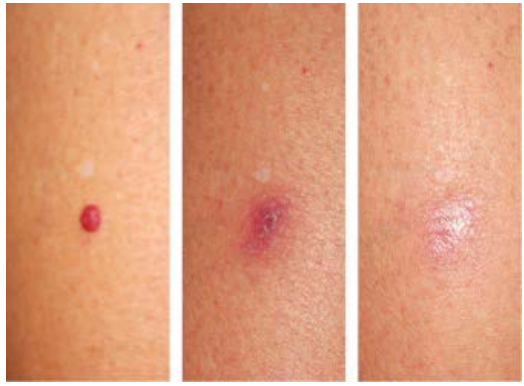

**Figure 15:** Pyogenic granuloma. Pretreatment picture, after 2 weeks and 1 month from the fourth and final treatment.

## The Use of the IPL for the Management of Acne Vulgaris

Acne vulgaris is a common inflammation of the pilosebaceous glands, characterized by comedones, papules, pustules, superficial cysts suppurate, inflamed nodules and, in extreme cases, fistulae and harvested tuberous suppurate, in the form of real pockets. Several factors are incriminated in its pathogenesis, including:

- An increase in sebum production induced by various factors (hormonal and food in particular)
- Abnormal desquamation of follicular keratinocytes
- Presence of a bacterial infection caused mainly by *Propionebacterium acnes*

Traditional therapy of acne vulgaris involves the combination of oral therapy (for example isoretinoina, antibiotics) and topical (for example triamcinolone acetonide, keratolytic agents). The therapy with bright radiation, recently introduced, offers a viable alternative because:

- Oral therapy involves numerous side effects
- Topical home therapy must be continued for a long time with more different products throughout the day
- Does not rule out the combination with the traditional therapy

There are numerous studies in the literature that testifies the validity of the treatment, especially in combination with ALA [20-25]. The light therapy can also be associated with medium peels with keratolytic activity (especially salicylic acid) with excellent results (Figure 16). The Protocol provides for alternate sessions twice a week (IPL - 15 days - peeling - 15 - IPL - ...). The target of the electromagnetic radiation is porphyrins produced by the bacterium *P. Acnes*. The absorption peak is between 430 and 490nm, and so you must use:

- A low cut-off filter (for example 430-1200)
- Long pulses (greater than 30ms)
- Low fluences
- Handpieces with large crystal size.

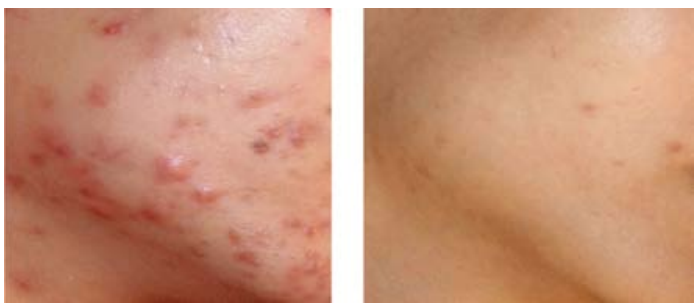

**Figure 16:** Acne vulgaris. Before and after treatment pictures combined with IPL, peels and topical therapy at home. Outcome at 3 months.

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## Chapter 12

# Laser Hair Removal

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## Abstract

The presence of unwanted hair is extremely distressing to patients and may impact their quality of life. So, the demand for a safe and effective cosmetic procedure in order to treat this condition is rapidly growing. A variety of laser devices and light sources are now available for hair removal, including long-pulsed alexandrite, long-pulsed Nd: YAG and diode lasers and broad-spectrum intense pulsed light sources. Any of these devices target melanin in the hair follicle. Therefore, the best candidate for laser hair removal is fair skinned with dark terminal hair. However, the proper selection of laser parameters such as wavelength, pulse duration and fluence coupled with an efficacious cooling system allow to treat also darker skin types with satisfactory results. A knowledge of hair follicle biology, laser-tissue interactions and laser safety are extremely important to optimizing treatment efficacy while reducing the risk of complications and adverse effects.

**Keywords:** Alexandrite Laser; Cooling System; Diode Laser; Fluence; Hair Follicle; Hirsutism; Hyperthricosis; Intense Pulsed Light; Laser Hair Removal; Melanin; Nd: YAG Laser; Phototype; Pulse Duration; Selective Photothermolysis; Spot Size; Unwanted Facial Hair; Wavelength

## Introduction

Unwanted Facial Hair (UFH) is a common condition. It is estimated that over 40% of the general female population experience some degree of UFH, ranging from biologically normal but undesirable to excessive unwanted hair related to an underlying pathology [1]. UFH is a particular concern not only for fertile women, but also for postmenopausal women. The reduction in ovarian hormones and increased androgen levels observed in menopause usually manifest with several symptoms, including hair disorder, such as the appearance of facial unwanted hair [2].

The presence of UFH is extremely distressing to patients and may impact on their quality of life. Women spend considerable time on the management of their facial hair. They feel uncomfortable in social situations, reporting high levels of emotional distress, anxiety and depression [3]. A recent review suggests a holistic treatment approach of this condition including evaluation of the implementation of emotional coping strategies and on-going support, lifestyle modifications, pharmacological interventions (to address underlying

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pathologies) and the use of cosmetic hair removal methods as either a stand-alone or adjunct treatment as appropriate to the individual [4]. Since the 1980s, laser technology has become increasingly popular to treat a variety of cutaneous conditions, including pigmented and vascular lesions, hair and tattoo removal. Laser hair removal is a rapidly growing cosmetic procedure. This chapter will focus on concepts about hair follicle anatomy and physiology, laser physics, laser-tissue interactions and laser safety. It will also provide a review of hair removal laser systems currently available for hair removal and clinical guidelines.

## Biology of hair follicle

The peculiar production of hair follicle in mammals fulfills a number of functions including sensory reception, protection against heat loss and environmental trauma. In humans, body hair has almost completely lost its protective value, but maintains some biological functions such as protection from actinic damage for the scalp and dispersions of sebaceous and apocrine gland products. However, the primary purpose of hair in human is its profound role in social interactions. Conditions like hair loss or excessive growth of unwanted hair can cause significant distress for patients.

Hair follicles are distributed throughout the entire skin surface with the exception of palms, soles and portions of the genitalia. According to size, hair can be classified into lanugo, vellus hairs and terminal hairs. Formation of lanugo hair is characteristic of the prenatal period: it's a dense, soft hair covering the fetal skin, usually shed before birth or early post-partum. Vellus hairs are fine, short and hypopigmented while terminal hairs are long, coarse and pigmented. The hair bulb of terminal hairs in anagen is located in the subcutaneous fat. The hair bulb of vellus hair in anagen is located in the reticular dermis. At birth terminal hairs are found on the scalp, eyelash and eyebrows and vellus hairs are found elsewhere; at puberty, under the influence of sex hormones vellus hair follicles transform into terminal hair follicles in areas like axillae, genitalia, trunk and beard in males [5].

## Anatomy

The hair follicle is composed of epidermal and dermal compartments and their interaction plays an important role in the morphogenesis and growth of the hair follicle [6]. Anatomically, the hair follicle is divided into three segments: infundibulum, isthmus, bulbar and suprabulbar region. The infundibulum extends from the insertion site of sebaceous gland duct to the skin surface. The isthmus is the portion of the follicle extending form the insertion of the arrector pili muscle, the bulge, to the opening of the sebaceous gland duct. The bulge is composed by cells which have the characteristic properties of epithelial stem cells, thus serving as a reservoir for epidermal and follicular cells [7]. The bulbar and soprabulbar region extends from the lower portion of the follicle to the insertion site of the arrector pili muscle. The bulb includes the matrix cells and the dermal portion of the follicle. The matrix consists of rapidly proliferating keratinocytes which, by growing upward, produce the hair shaft and the inner root sheath.

Pigment in the hair shaft is produced by melanocyte stem cells, located in the bulge, that give rise to mature melanocytes which synthesize and secrete hair pigments during anagen phase. Loss of hair pigment resulting in graying of hair is one of the features of ageing. Age-associated hair graying may be due to melanocyte stem cells depletion caused by UV radiation and genotoxic reactive oxygen species [8].

The dermal portion of the hair follicle can be divided into two compartments, the dermal papilla and dermal sheath. The dermal papilla is located at the base of the hair follicle. The dermal sheath lines the epithelium of the hair follicle from the bulge level downward and is

contiguous with the base of the dermal papilla through a stalk. Cells within dermal papilla and dermal sheath are specialized fibroblasts of mesenchymal origin [9].

### Hair Cycle

During postnatal life, hair follicles are characterized by continuous cycles of growth and rest, during which they undergo anatomic and metabolic changes. The hair cycle consists of three phases: a growth phase (anagen); a transitional or regression phase (catagen), and a resting phase (telogen). In humans, each follicle has its own inherent rhythm, so hair grows in an asynchronus manner. The duration of each phase and the proportion of hairs growing during each phase vary considerably depending on age, gender, body site, hormone and underlying genetic susceptibilities. For instance the anagen phase lasts 2-6 years in scalp hair with 85-90% actively growing hairs; on the legs it lasts 5-7 months and on the arms 2-4 months with approximately 20% active hair growth [10]. The anagen phase involves the complete regeneration of the lower portion of hair follicle. It begins with the activation of secondary hair germ, a cluster of epithelial cells at the base of telogen follicle. In early anagen, these epithelial cells rapidly proliferate and differentiate into the inner root sheath and the hair shaft. The new follicle penetrates deeper into the skin to the level of the subcutaneous fat. The duration of anagen cycle dictates the shaft length which is different from one anatomic site to another. The molecular signals responsible for the onset of anagen are still unclear; however, interactions between dermal papilla and follicular epithelium seem to play a critical role for this process [11]. The catagen phase is a highly controlled process of apoptosis of epithelial cells in the bulb and outer root sheath, the outermost epithelial layer, consisting of the dramatic cessation of cell growth and differentiation, release of the papilla from the bulb, loss of differentiation of lower follicle [12]. The first sign of regression in catagen is the withdrawal of follicular papilla from the basament membrane. Matrix keratinocytes stop proliferating and undergo apoptosis. The result is the involution of the lower follicle; the fibrous sheath contracts, followed by the papilla, which remains close to the bulge, while the follicle enters the telogen phase.

In the telogen phase, hair follicles are very short in length and lack of pigment-producing melanocytes and the inner root sheath. Recently, the hair shaft shedding from the telogen follicle has been described as a distinct cycle phase, known as exogen, and proposed to be an active process relating also to signaling or structural changes proceeding to hair shaft release which is thought to regulate the process [13].

The control of the hair cycle remains still unclear. During hair follicle cycle, interactions between epidermal and dermal compartments are regulated by a distinct set of molecular signals that are unique for every distinct phase of the hair cycle. In telogen hair follicles, epithelial-mesenchymal interactions are characterized by a predominance of inhibitory signals that retain the hair follicle in a quiescent state. During anagen, growth stimulatory pathways are activated in the epithelium and in the mesenchyme, the coordination of which are essential for proper hair fiber formation. During catagen, apoptosis in the hair follicle epithelium is caused by the termination of anagen-specific epidermal-dermal interactions [14].

## Conditions Characterized by Excessive Hair Growth: Hirsutism and Hyperthricosis

Hirsutism is defined as the presence in women of terminal hairs in areas of the body where hair growth is under androgen control, such as beard and moustache, chest, abdomen and inner thigh. Hirsutism affects between 5% and 10% of women of reproductive age [15].

Androgenic causes are responsible of hirsutism in up to 80% of patients. Non-androgenic causes of hirsutism are relatively rare. Polycystic Ovary Syndrome (PCOS) is

the most common cause of hirsutism. In approximately 1-8% of the women with hirsutism, the underlying cause is 21-hydroxylase-deficient Non-Classic Adrenal Hyperplasia (NCAH), whereas about 3% of hyperandrogenic women suffer from Hyperandrogenic-Insulin Resistant Acanthosis Nigricans (HAIRAN) syndrome. Idiopathic Hirsutism (IH) constitutes 5-17% of the patients with hirsutism. More rare causes include glucocorticoid resistance syndrome, hyperprolactinemia, acromegaly, Cushing's syndrome and some drugs [16].

After the menopause, there is a slow physiological depilation in most women, with the exception of facial hair, which tends to increase. Hirsutism becoming rapidly worse or starting at other times of life may be caused by androgen excess from neoplasia.

Hypertrichosis is defined as an increased hair density or lenght beyond the accepted limits of normal for a given age, sex or race, excluding androgen-induced hair growth. Hypertrichosis may be an isolated finding or associated with a syndrome, be associated with additional congenital anomalies or a marker for systemic disease. In order to diagnose it accurately, the age of onset, type, localization and pattern of hair growth, associated disorders, medications and perhaps associated anomalies and family history should be considered [17].

**Evaluation of women presenting with excessive hair growth**

The diagnostic evaluation of patients with excessive hair growth first involves confirming the presence of hirsutism by a clinical history, which takes into account ethnic differences and a physical examination, as many women with unwanted hair do not actually have terminal hair growth in a male-like pattern [18]. The physical examination should establish the type, pattern and extent of the excessive hair growth. The most common method of scoring hirsutism is the modified Ferriman-Gallwey scale [19].

Secondly, associated or etiological disorders should be excluded (e.g. ovulatory dysfunction, adrenal hyperplasia, diabetes, thyroid hormone abnormalities).

Recently, an interdisciplinary group of leading experts met to discuss and address the challenge of developing clinical practice guidance for the evaluation of hirsutism in premenopausal women. The outcome of the discussions was an evaluation form to be used by the clinician to help evaluate a patient presenting with excessive hair growth [20].

## Treatment of Unwanted Facial Hair

Treatment of hirsutism generally involves two approaches: the treatment of underlying disorders, where diagnosed, and the mechanical/cosmetic improvement or destruction of visible hair.

Several methods of hair removal are available, each with varying degrees of cost, efficacy, and side effects. Shaving is a useful and safe method of facial hair removal but often psychologically unacceptable to women [21]. Using depilating agents, although useful, may result in chemical dermatitis and, occasionally, allergic dermatitis [22]. Plucking or waxing in androgenized skin area should be discouraged because these techniques can induce folliculitis and trauma to the hair shaft with subsequent development of ingrown hairs and further skin damage [18]. Electrolysis is a technique that allows a long-term hair removal, but it is costly and time-consuming, and largely has been supplanted by the use of laser and intense pulsed light source devices [21].

## Laser Hair Removal

The mechanism of action of laser and intense pulsed light source devices is based on the theory of selective photothermolysis. This theory states that it is possible to induce a

thermal damage of a specified target using wavelength of light preferentially absorbed by a target chromophore and delivering energy within a period shorter than or equal to the Thermal Relaxation Time (TRT) of the chromophore in order to avoid the spread of thermal energy to surrounding structures [23]. TRT is defined as the time it takes a target to cool to 50% of its maximum absorbed thermal energy after laser irradiation.

For hair removal, the chromophore within the target structures is provided by melanin located in the hair follicle. When using laser light to achieve a follicular damage, three parameters need to be considered: wavelength, pulse duration and fluence. It is also especially important to consider spot size and the use of a cooling method.

Two factors play a significant role in the choice of the appropriate wavelength in laser hair removal: the absorption spectrum of melanin and the depth of the hair matrix. Therefore, it is very important the selection of a wavelength that allows good dermal penetration (the hair matrix is located 3-5 mm under the skin surface) and adequate absorption by the melanin in the hair follicle. Melanin has a broad absorption band ranging across ultraviolet, visible and near infrared spectrum with decreasing absorption as the wavelength increases [24]. Wavelengths ranging between 700 and 1100 nm are broadly absorbed by melanin, with poor absorption by competing chromophores like oxyhemoglobin and water. Also, these longer wavelengths achieve deeper penetration, thus allowing targeting deeper structures. Therefore, any laser system or light source emitting light in this region of electromagnetic spectrum may be used for hair removal.

TRT of hair follicle ranges from 10 to 100 msec. Therefore, the ideal pulse width for laser epilation should lie between the TRT of epidermis (3-10 msec) and TRT of hair follicle (10-100 msec). However, further considerations are necessary when selecting pulse duration in hair removal. The hair follicle represents a complex unit where different structures should be targeted in order to achieve significant hair damage. These structures are not uniformly pigmented, including areas highly absorbing such as melanin-bearing hair shaft and the matrix cells, and bulge area, where stem cells are located, characterized by absence of melanin. So, a novel concept of selective thermal damage of non-uniformly pigmented structures has been formulated. The theory, known as extended theory of selective photothermolysis, states that in case of non-uniformly pigmented targets, it is possible to achieve a significant thermal damage by heat diffusion from the pigmented area using a pulse duration significantly longer than the TRT [25]. New laser devices allowing selection of different pulse duration ranging from 3msec to 100msec are nowadays available on the market.

The energy delivered to the target must be sufficient to achieve follicular destruction. A study performed to evaluate histological alterations in hair follicles after laser exposure showed heterogeneous follicular damage, related to variations in follicular melanin concentration, and a fluence-dependent thermal injury [26]. A confirmation of these results is reported in the study of Lin et al., showing that intermediate fluences can induce non-scarring alopecia, whereas high fluences induce scarring alopecia [27]. Some studies investigated the efficacy of using low fluences in order to reduce the risk of complications without compromising the results. Roosen et al., have investigated the effect of repeated low fluence photoepilation with Intense Pulsed Light (IPL) on biopsies and cultured human hair follicles. Single pulses of IPL with a fluence of 9J/cm2 and duration of 15 milliseconds were applied to one lower leg of 12 female subjects, followed by taking a single biopsy per person, either immediately, or after 3 or 7 days. The majority of the cultured follicles that had been exposed to low fluence treatment showed a marked treatment effect. The part of the bulb containing melanin was the target and a catagen-like transformation was observed. The other follicles that had been exposed to low fluence showed a less strong or no response. The skin biopsies also revealed that the melanin-rich region of the hair follicle

bulb matrix was targeted; other parts of the follicle and the skin remained unaffected. The authors concluded that low fluence photoepilation targets the pigmented matrix area of the anagen hair follicle bulb, causing a highly localized but mild trauma that interrupts the hair cycle, induces a catagen-like state and eventually leads to temporary loss of the hair [28]. However, several studies have been published reporting the advantages of laser hair removal at lower fluences without affecting clinical efficacy [29-31].

In addition to fluence and pulse duration, another parameter that should be adjusted during a laser hair removal session is the spot size. Once the light penetrates into the dermis, the depth of penetration is almost totally dominated by the phenomenon of dermal scattering. A consequence of this phenomenon is the radial spreading of the beam with subsequent reduction of its intensity as it penetrates deeper into the skin. It has been demonstrated that dermal scattering is affected by the spot size [32]. When light is applied to skin using a small spot size, the scattering diffuses the beam rapidly. The fluence decays as a function of depth, so that most of energy is dissipated in radial direction and cannot reach the bulb. Using a larger spot size allows reducing dermal scattering, leading to greater depth of penetration of the beam and lowering threshold fluence [30].

Although follicular melanin is the primary target for laser epilation, its presence in the epidermis represents a competing chromophore for laser energy absorption. Using active cooling during laser hair removal allows to limit heat accumulation in the epidermis, thus minimizing collateral damage and reducing discomfort to the patient. Moreover, the use of a cooling system permits delivery of higher fluences needed to an effective epilation. Cooling methods commonly used include gel cooling, cryogen cooling, contact cooling and forced air cooling.

## Laser Devices

A number of lasers and light devices are now available for the treatment of unwanted hair. They include long-pulsed alexandrite laser, diode laser, Neodymium: YAG (Nd: YAG) laser and IPL.

### Long Pulsed Alexandrite Laser

Long-Pulsed Alexandrite Laser (LPA) is a solid state laser that emits light at a wavelength of 755 nm. This wavelength allows a greater depth of penetration but less melanin absorption when compared to ruby laser (694nm). This feature should make LPA systems relatively safe in darker skin types, with less risk of post-treatment side effects compared to ruby laser. The clinical efficacy of LPA has been evaluated in several studies with a reported success rate ranging from 35 to 80% at 6 months after 3 or more sessions [33-36]. The results vary depending on the body area, with maximum reductions observed for sites like axillae and bikini line. Generally patients who undergo more treatment sessions achieve a higher rate of hair reduction. LPA laser has been reported to be safe for hair removal also in Fitzpatrick skin types IV-VI, with complications occurred in only 2% of cases [37]. Aldraibi et al., reported that a 3-msec alexandrite laser provides a safe and effective treatment in patients with skin types IV and V, but is less safe in skin type VI. They also observed that using a class I topical corticosteroid cream 10 minutes prelaser and twice a day for 5 days postlaser can help to minimize post-treatment erythema and edema and also decreases the duration of hyperpigmentation [34]. Common complications after LPA laser epilation include perifollicular edema and erythema that usually resolve rapidly within 1-4 hours. In darker skin types or in tanned skin blistering, crust formation, hyperpigmentation and hypopigmentation may occur. These complications are generally transient. Uncommonly reported side effects after laser epilation with LPA include de-novo growth of hair outside the area treated by laser, potentiation of co-existing vellus hair in the treatment area,

induction or aggravation of acne, premature grayness of hair, tunneling of hair under the skin, prolonged diffuse redness and edema of the face, focal hypopigmentation of the lip, angular cheilitis, allergic reaction to the cooling gas, and inflammatory and pigmentary changes of pre-existing nevi [38]. Persistent urticaria is a rare side effect of laser epilation. Rupture of hair follicle by laser heat may trigger a delayed hypersensitivity reaction in a subset of predisposed allergic patients. To prevent this complication, Landa et al., suggests that laser epilation in allergic patients should be preceded by an extended laser patch test, which should be evaluated 24-48 hours later. Preventive prednisone should be prescribed to patients who develop an urticarial rash on the test area [39].

## Diode laser

Diode lasers emit light at 800-810nm wavelength. Although light at this wavelength is not as well absorbed by melanin as the 694nm ruby and 755nm alexandrite wavelengths, the longer 800nm wavelength penetrates deeper into the hair follicle thus allowing to damage follicular growth centers. Moreover because of this longer wavelength, diode lasers permit to treat more safely individuals with darker skin types. The clinical efficacy of an 810-nm diode laser has been evaluated in the treatment of unwanted hair in individuals with Fitzpatrick skin types II-IV. A mean removal efficiency of 74% and 79% was noted at 3 and 6 months, respectively, and was best in individuals with skin type III [40]. A retrospective study performed by Kopera has evaluated the long-term efficacy of a solid state; 800nm pulsed near infrared diode laser system for the reduction of pigmented hair, and extending habitual hair plucking intervals. In 48 months 242 patients received diode laser treatments on 477 sites. Treatment data and an anonymous patient questionnaire on data concerning undesired hair growth (eg., predisposition, psychological aspects), and hair plucking habits have showed that after an average of 1.97 treatments (range 1-6) sufficient reduction of pigmented hair was achieved for a mean period of 8.1 months. The habitual hair plucking interval was raised from a mean of 3.69 days before treatment to 15.19 days after laser epilation [41]. A study comparing the clinical and histologic efficacy, side effect profile, and long-term hair reduction of long-pulsed diode and long-pulsed alexandrite laser systems was undertaken by Handrick and Alster [42]. Twenty women with Fitzpatrick skin types I-IV and dark terminal hair underwent three monthly laser-assisted hair removal sessions with a long-pulsed alexandrite laser (2-msec pulse, 10mm spot, 25J/cm2 ) and a long-pulsed diode laser (12.5msec or 25msec, 9mm spot, 25-40J/cm2). Optimal clinical response was achieved 1 month after the second laser treatment, regardless of the laser system or fluence used. Six months after the third and final treatment, prolonged clinical hair reduction was observed with no significant differences between the laser systems and fluences used. Histologic tissue changes supported the clinical responses observed with evidence of initial follicular injury followed by slow follicular regeneration. Side effects, including treatment pain and vesiculation, were rare after treatment with either laser system, but were observed more frequently with the long-pulsed diode system at the higher fluence of 40J/cm2. In 2002 Rogachefsky et al., have performed a study to evaluate the clinical efficacy and side effect profile of a modified 810 nm diode laser device operating in a super-long-pulse mode (200-1000msec). Ten female subjects with Fitzpatrick skin type's I-VI received either one or two laser treatments at eight test sites. Subjects were evaluated 6 months after the first treatment. Subjects were evaluated for hair removal efficiency, optimal pulse duration and delivered fluence, and associated complication rate. Optimal hair reduction at 6 months (31%) was achieved at a thermal diffusion time of 400msec (46J/cm2), the pulse duration at which heat diffusion and thermal damage to the follicular stem cells reaches its peak. Highest complication rate was found at 1000 msec pulse duration and 115J/cm2 fluence [43]. A study by Zins et al., evaluated patient satisfaction with hair removal using a diode-

laser system. A self-administered survey was mailed to 220 patients who underwent treatment between 2000 and 2004. 80% of patients were either "very satisfied" or "somewhat satisfied." 40% of patients felt they achieved 75% hair reduction and 38% reported 50% hair reduction. The majority of patients required 5-6 treatments over 13-18 months for maximum improvement. The majority of patients (91%) experienced no long-term side effects [44]. The effects on hair structures of a new diode laser technology that incorporates low fluence but very high average power were investigated by Trelles et al., in patients with darker skin types. The treatment technique employed multiple, in-motion, repetitive laser passes on a 100 cm2 area of the skin. The histologic examination revealed inflammatory infiltrate, hair shaft detachment from its sheath, and perifollicular oedema, related to incipient necrosis [29]. A multicenter study of hair removal with the same technology was carried out on 368 patients (phototypes III to V) to test its efficacy in a 6-month follow-up after five treatments on the face and various body areas. Results obtained a high degree of patient satisfaction and a low index of adverse events [45].

The most common side effects of diode laser hair removal include transient erythema, perifollicular edema, pain, folliculitis, hyper-pigmentation, hypopigmentation, and crusting.

## Long pulsed Nd: YAG Laser

Long-Pulsed Nd: YAG laser generates a 1064 nm wavelength beam. Melanin absorption at this wavelength is much less compared to LPA and diode lasers. However, the Nd: YAG laser beam is able to penetrate more deeply into the dermis. The first study evaluating the efficacy and safety of a long-pulsed Nd: YAG laser was performed by Bencini et al., 208 subjects were treated during an 11 month period. Treatment sessions were performed with a fluence of 23-56J/cm2 at 1-month intervals until obtaining desirable results. Follow-ups ranging from 1 to 6 months showed a prolonged epilation with no relevant side effects [46]. Lévy et al., evaluated the efficacy of the long-pulse Nd: YAG laser in removing unwanted facial hair. The average reduction of in the hair count was 43% at 3 months, 36% at 6 months, and 46% at 9 months. No significant complications were observed in the range of skin types treated, even in the darker skin types [47]. In a study of 2004, 36 patients (skin type's I-VI) with dark terminal facial or nonfacial hair were treated with a long-pulsed Nd: YAG laser (1064nm, 10-mm spot size, fluence of 30 to 60J/cm2). The selected pulse duration was dependent on the skin type of the patient: Skin types I/II, III/IV, and V/VI received 10, 20, and 30ms, respectively. Three consecutive laser treatments were performed at 4- to 6-week intervals. Peak hair reduction was observed 1 month after the series of laser treatments with a mean hair reduction ranging from 58% to 62% on facial sites and 66% to 69% on nonfacial sites. At 6 months follow-up, a mean hair reduction of 41% to 46% on the face and 48% to 53% on the body was found. Adverse reactions included mild to moderate treatment pain, short-term erythema, and rare occurrences of transient pigmentary alteration without scarring [48]. Recently, Rao et al., have collected retrospective data from 150 individuals with Fitzpatrick type IV-VI skin who underwent hair removal with long-pulsed Nd: YAG laser. Data included area treated, fluence, and number of treatments, outcome, patient satisfaction and complications. The most common phototype was type IV (94%). The most frequently treated area was the face (84.7%) followed by the underarms and legs. The mean number of treatments was 8.9 (range 4-22). The maximum fluence averaged 26.8J/cm2 and was significantly higher for facial hair. Of the patients, 78.7% felt that their treatment was good or satisfactory. Mean hair reduction was 54.3%. Satisfaction from the treatment was significantly higher in individuals undergoing treatment of non-facial areas. Subsequent hair growth was slower and finer in 79.3% of the patients. There were no complications in 86% of the patients. All the complications were transient, with hyperpigmentation being the most frequent complication [49].

### Intense Pulsed Light (IPL)

IPL devices are high intensity pulsed sources that deliver incoherent light in a broad wavelength spectrum of 500-1200 nm. Using different cut-off filters (515-755nm), shorter wavelengths can be eliminated, thus allowing that the optimal wavelengths to pass to correspond to the depth of target structures. The properties of IPL systems allow a great variability in the selection of treatment parameters, thus permitting adaptation to the treatment to the patient's skin type. Light is delivered to the skin through quartz or sapphire light guide; a transparent cooling gel is usually applied prior to the treatment to protect the epidermis from excessive heating. The efficacy of IPL in hair removal has been reported in several studies [50-51]. A five year experience with IPL was reported by Lor et al., The satisfaction in 207 patients with unwanted facial and body hair was evaluated through a questionnaire. 45 (22%) of patients were very satisfied, 93 (45%) were satisfied and 69 (33%) remained unsatisfied with the outcome of light-assisted hair removal. Hair-free periods from weeks to years could be observed [52]. In a study of 2005, hair removal using IPL was performed on 108 consecutive patients. Eighty of these patients answered a questionnaire. The investigated parameters were hair and skin type, number of pulses, fluence, pulse duration, pulse delay, the filters used, and the treated area. The patients had between 1 and 13 treatments most of them during 2 to 6 sessions. Patients who underwent fewer treatments (1-3 treatments) were more satisfied compared with those who had more than 7 treatments. 60% of the patients rated their satisfaction to be good to excellent. 67% of the patients reported no complications. Side effects commonly reported were prolonged erythema (16.25%), blisters (6.25%), and temporary hyperpigmentation (8.75%). An increased number of complications and a decreased satisfaction rate were noted with darker skin types, but it was not statistically significant. To minimize the risk of side effects the authors suggest that IPL parameters should be adjusted at every treatment session according to the skin response at the previous one [53]. Radmanesh et al., investigated the side effects of IPL hair removal therapy among 2541 female hirsute patients. Patients were treated every 4-6 weeks and for eight sessions or more. All patients were followed for up to 20 months. The parameters were chosen according to the patients' Fitzpatrick skin types and tolerance. The cut-off filters commonly used were 695, 755, 645 and 615 nm in descending order of their frequencies. Burning and its sequelae (post-inflammatory hyperpigmentation, post-inflammatory hypopigmentation, bulla and erosion), leukotrichia, paradoxical hypertrichosis and folliculitis are four major side effects of IPL hair removal therapy reported in this study [54].

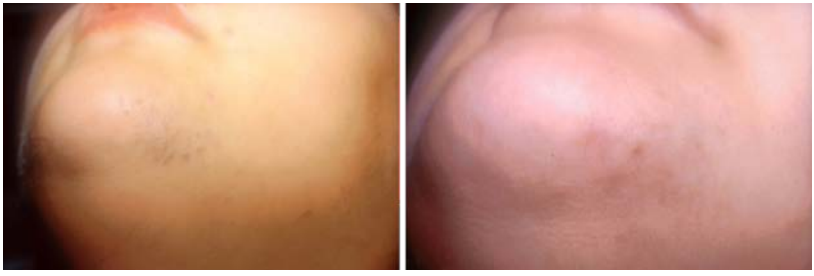

**Figure 1:** Pre and Post treatment - two session with IPL Lumenis M22 (640 nm, two impulses).

## Comparison of Laser and Intense Pulsed Light Assisted Hair Removal

Several studies have compared the efficacy and safety of the different laser and light sources available for laser hair removal. A retrospective study of 805 consecutive laser-

assisted hair removal treatments was conducted on 75 patients using a long-pulsed Nd: YAG, a long-pulsed alexandrite, or a long-pulsed diode laser. All patients were evaluated at least 3 months after the last treatment. The mean hair reduction was 42.4%, 65.6%, and 46.9% in Nd: YAG, alexandrite, and diode lasers, respectively. When considering the number of treatment sessions, the efficacy of alexandrite and diode lasers was not significantly different, whereas both systems were more efficacious than Nd: YAG. Neither of the laser systems showed better results for a particular skin type. The occurrence of side effects was not significantly different between three laser systems [55]. Clinical trials were conducted on 232 individuals using diode and alexandrite laser and IPL for hair removal. The optimal result has been achieved with a number of sessions between 3 and 7. At 6 month follow-up, optimal hair reduction was observed with no significant differences between the light sources, but a hair reduction was found to be higher using the diode laser. Side effects were observed with all light sources but more frequently with diode [56]. In 2006, Amin et al., have compared the efficacy of four systems for laser hair removal. 10 subjects (skin type's I-III) underwent treatment of unwanted hair on the back or thigh. All were treated twice with an intense pulsed light with a red filter; an intense pulsed light with a yellow filter; an 810 nm diode laser; and a 755 nm alexandrite laser. Four treatment areas as well as a control non-treated area were selected. Each treatment area was evaluated with a camera system specifically designed for hair counts at 1,3 and 6 months after the second treatment by a blinded non-treating physician. Evaluation of photographs at 1, 3, and 6 months revealed a significant decrease in hair counts (approximately 50%) and hair coverage (approximately 55%). There was no statistical difference in efficacy between the four different light devices. Minimal transient adverse effects were reported for all devices [57]. Recently, a randomized, controlled clinical trial has been performed on two groups of 57 and 54 women. One group was treated with alexandrite laser alone (four sessions, two months apart). The other group was treated sequentially with diode laser for the first two sessions and alexandrite laser for the next two sessions. There was no significant difference regarding mean of hair reduction between the two groups during the courses of treatment. Comparison between the two groups showed no significant difference one month, three months and six months after the last treatment [58]. An evidence-based review of hair removal using lasers and light sources was conducted in 2006. A total of 9 randomized controlled and 21 controlled trials were identified in Medline and the Cochrane Library. The best available evidence was found for the alexandrite and diode lasers, followed by the ruby and Nd: YAG lasers, whereas limited evidence was available for IPL sources [59]. A systematic review of the clinical trials with use of various laser sources for hair removal conducted in 2009 revealed that hair reduction at least 6 months after the last treatment was 57.5%, 42.3%, 54.7%, and 52.8% after three sessions for diode, Nd: YAG, alexandrite and ruby, respectively [60]. Sochor et al., have compared the hair removal efficacy of three methods: intense pulsed light, a combination of IPL and radio frequency and diode laser. Forty patients were treated within three standardized squares on lateral sites on their legs. Each of these squares was treated twice with an interval of 4-6 weeks. The fourth square was left as a control. A blinded physician counted the hairs in each square before the first treatment and 8 months after the second treatment. The mean hair count reduction was 49.90%, 39.16% and 47.15% for diode laser, IPL and IPL+RF, respectively [61]. More recently, Klein et al., have conducted an intra-patient, left-to-right, assessor-blinded and controlled trial comparing a diode laser with IPL. 30 participants (skin type II-III) with unwanted axillary hair growth underwent 6 treatments with each device in 4-week intervals. Final assessment was conducted 12 months after the last treatment by means of hair counts using close-up photographs. A significant hair reduction was achieved with both devices. Mean reductions from baseline (3 and 12 months after the last treatment) were 59.7% and 69.2% for diode laser and 42.4% and 52.7% for IPL [62].

### Complications of laser-assisted hair removal

Complications associated to laser-assisted hair removal are related to unwanted epidermal and/or thermal damage due to partial absorption of the laser energy by melanin in the epidermis. Obviously, patients with darker skin types are more likely to experience some laser complications due to the greater absorption of light in the epidermis. Most common side effects are generally temporary. Erythema and edema are commonly seen after laser treatment, usually lasting for about 48 hours. Postinflammatory pigmentary changes include hypopigmentation and hyperpigmentation. Hypopigmentation is commonly transient, although it may last for many months. It is thought that hypopigmentation after laser exposure is related to the suppression of melanogenesis in the epidermis, rather than the destruction of melanocytes [63]. Pigmentary changes after alexandrite laser hair removal were reported by Weisberg et al., Seven patients developed a similar pattern of initial hyperpigmented rings, later developing into a thin wafer-like crust followed by hypopigmentation with gradual return to their normal skin color [64]. Hyperpigmentation seems to be related to melanocytic stimulation similar to a UV-induced suntan [65]. It is generally a temporary effect that responds to time and to topical therapy with bleaching agents. Other side effects that can be seen after phoepilation include blister and crusting formation, folliculitis and leukotrichia [54]. A rare but significant adverse effect with laser hair removal is paradoxical hypertrichosis. In 2010, Desai et al., have published the results of an analysis of case studies and review articles from literature along with their own experience regarding this side effect. They reported a low incidence of paradoxical hypertrichosis, ranging from 0.6% to 10%, and most commonly occurring on the face and neck. The condition was observed with all laser and light sources especially in individuals with darker skin types (III-VI), with dark, thick hair and with underlying hormonal conditions. Possible causes included the effect of inflammatory mediators and subtherapeutic thermal injury causing induction of the hair cycle [66]. When this side effect occurs, the treatment is laser therapy of the affected area.

## Clinical Guidelines

### Indications

Laser-assisted hair removal is indicated in any patient affected by excessive hair growth as well as in individuals who want to remove hair on the body for cosmetic reasons. Another indication is chronic pseudo folliculitis.

### Patient selection

The ideal candidate for laser hair removal is a light-skinned individual with dark terminal hair. The treatment of darker skin types is particularly challenging because of the greater absorption of laser energy by epidermal melanin. To minimize the risk of complications after laser exposure in darker skin types, longer wavelengths and pulse durations coupled with efficient cooling devices should be considered. The safest laser system to treat dark-complexioned skin individuals is long-pulsed Nd: YAG. A recent study has evaluated patient satisfaction and complications in 50 patients with Fitzpatrick skin type VI who had been treated with long-pulsed Nd: YAG for unwanted hair. The mean satisfaction score was 84.2. Hyperpigmentation after treatment was noted in three patients (6%), which lasted for 3-10 days. No hypopigmentation, blistering, or scarring was observed [67]. Contraindications to laser treatment include patients with associated photo-aggravated skin pathologies such as systemic lupus erythematosus and active cutaneous infections in treatment area. Caution should be exercised in patients with keloids and keloidal tendencies, patients on long-term drugs that cause the skin to be more sensitive towards light, like minocycline and

isotretinoin, patients with unrealistic expectations, psoriasis and vitiligo patients because of the risk of Koebnerization of treated area and patients with previous history of herpes simplex [68]. Regarding the age limit to performing laser hair removal in children there is no consensus. An experience of laser hair removal in 24 children under 16 years was reported by Rajpar et al., The mean age at first treatment was 12.3 years. For patients with Fitzpatrick skin phototype II-IV, the lasers used were a long-pulse alexandrite. For patients with Fitzpatrick skin phototype IV-VI, lasers used were a long-pulse Nd: YAG. One patient required a general anaesthetic, eight required topical anaesthetic cream, and 15 did not require any form of anaesthesia. Intolerable discomfort requiring adjustment in fluence was the only recorded side-effect, affecting two cases. The authors concluded that when administered appropriately, laser hair removal is safe and well tolerated in children aged less than 16 years [69].

### Patient information and consent

Appropriate management of patient's expectations is very important when consulting the patient prior to start a laser treatment. To date, no method of 100% permanent hair eradication is available. So, the patient should understand the right meaning of the definition of "permanent hair removal". The United States Food and Drug Administration (FDA) have defined permanent hair removal as: "the long-term, stable reduction in the number of hairs re-growing after a treatment regime, which may include several sessions. The number of hairs regrowing must be stable over time greater than the duration of the complete growth cycle of hair follicles, which varies from four to twelve months according to body location". This means that although laser treatments will permanently reduce the total number of hairs, they will not result in a permanent removal of all hairs [32].

The patient should also be informed that multiple treatment sessions may be needed to achieve long term results. The treatment frequency depends on many factors such as the area to be treated. In the European Society for Laser Dermatology guidelines, it is recommended to perform treatments every 4-8 weeks [70]. Contraindications, possible side effects and complications should be discussed and the consent form filled in before starting the treatment.

### Preoperative treatment care

In order to obtain the optimal result and to reduce the risk of side effects, the patient must be advised to get the palest skin colour possible. Therefore, the patient should avoid sun exposure and use a broad-spectrum sunscreen for at least 4 weeks before the treatment. A bleaching cream such as hydroquinone may be considered in patients with darker skin types. No plucking, waxing, or electrolysis should be performed before laser hair removal because the light needs the melanin in the hair shaft as a chromophore in order to induce follicular damage. The growing hair should be cut or shaved or treat with a depilatory cream to avoid laser energy absorption by melanin within hair above the skin surface. The area to be treated should be cleaned and any makeup removed before starting the session. Benign melanocytic lesions should be covered with a white tape or pen to avoid light absorption. As photoepilation is a painful procedure, topical anaesthetic cream could be applied. Prior to starting the session, every person in the treatment room should wear safety goggles designed for the specific wavelength or range of wavelengths emitted by the light source.

## Epilation Treatment

Before starting the treatment, laser parameters have to be selected and adapted to the clinical situation and the patient skin type. Parameters like wavelength and pulse duration may affect the efficacy of the laser treatment and the risk of side effects. A laser with a

longer wavelength and longer pulse duration is less likely to be absorbed by epidermal melanin. Therefore it will be the choice when treating darker skin types. Hair color and skin color determine the best fluence to be used. Higher fluences reach higher degree of hair reduction. As the fluence is the main parameter causing adverse effects by overheating the surrounding tissue of hair follicles and the epidermis, it is suggested to start every treatment with appropriate conservative fluence levels. In order to reduce the risk of side effects while maintaining the efficacy of the treatment, larger spot sizes and adequate cooling system should be preferred. The ideal immediate response to laser treatment is coagulation of the hair shaft followed by diffuse erythema that resolves in 10 to 60 minutes. Effective laser epilation will result in some perifollicular edema that is not a side effect but a clear sign of thermal damage of the hair follicle and therefore a marker of the treatment endpoint. The edema occurs in few minutes and may last for few hours.

After the treatment the application of a topical corticosteroid will help to reduce erythema and swelling. Sun exposure must be avoided and the patient should wear a broad-spectrum sunscreen for 2 weeks after the treatment. If adverse effects as blistering and crusting occur they can be treated with an antibiotic cream and emollient cream.

### Physician qualification

The physician using photoepilation should have completed residency training in an appropriate specialty such as dermatology and a basic knowledge of laser physics, laser-tissue interactions and laser safety. Proper hands-on training of any system is mandatory before a dermatologist actually starts doing it. The physician should be familiar with early recognition, prevention and treatment of laser adverse effects.

### Safety precautions

As all hair removal systems are designed for deep penetration and strong absorption in melanin, they have a high potential for eye injury. In literature cases of ocular complications such as anterior uveitis as well as irreversible damage to the iris after laser-assisted eyebrow epilation are reported [71]. Therefore, treatment of the eyebrow is not recommended and proper eye protection is necessary for all persons within the operating room.

Although laser or IPL has no impact on pregnancy, most laser manufacturers exclude the use of photoepilation in pregnant women in their application notes.

## Treatment of Non-Pigmented Hair

Being the melanin the target chromophore of laser and IPL hair removal devices, the treatment of white, blond and red hair is extremely challenging. Goldberg et al., have reported the results of the treatment of terminal and vellus non-pigmented hairs with an optical/bipolar radiofrequency energy source-with and without pre-treatment using topical aminolevulinic acid. In this study, 10 females with white terminal hairs and 5 females with fine facial vellus hairs were treated twice at 4-6 week intervals with a combined optical bipolar radiofrequency source. At each treatment half of the treatment area was pre-treated with topical aminolevulinic acid; the other half was not. At a follow-up visit 6 months after the second treatment an average terminal white hair removal of 35% was observed using the combined pulsed light bipolar radiofrequency device. When pre-treatment with topical aminolevulinic acid was provided, the average hair removal of terminal white hairs was found to be 48%. None of the five subjects with vellus hair were noted to respond to either treatment [72]. In 2007, a randomized, controlled, double-blind study evaluating melanin-encapsulated liposomes as a chromophore for laser hair removal of blond, white, and gray hair was conducted. 16 patients with blond, gray, or white facial and body hair were treated

with a liposomal melanin spray (Liposome) and 3 sessions of 800 nm diode laser at intervals of 8 weeks (28-40J/cm). A control group of 16 patients applied physiological saline spray before diode laser treatment. Hair regrowth was measured 8 weeks after each session and additionally 6 months after the last treatment by hair count compared with baseline pretreatment values. Mean regrowth in the liposomal melanin group was 83% after 3 treatment cycles. At 6 months follow-up, average terminal hair count showed 14% reduction compared with baseline pretreatment thus making the clinical outcome unsatisfactory [73]. More recently, the results of a randomized clinical trial of hirsute patients with excessive facial white hair treated with combined coloring and IPL have been reported. The patients were randomly assigned to have their white hair colored with either black eyeliner or black hair dye. Then they underwent 6 sessions of IPL with a 4-week interval. Evaluations were made after the last treatment. In the eyeliner group 48.4% of patients showed a fair response, and 51.6% of patients showed a good response. In the color-dye group 3.2%, 54.8% and 41.9% of patients scored poor, fair, and good, respectively. There were no differences in clinician judgment of the treatment success between the eyeliner and color-dye groups after the 6 sessions [74].

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## Chapter 13

# The Carbon Dioxide Laser in Dermatologic Surgery and Facial Rejuvenation

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## Abstract

Invented in 1964 by Kumar Patel of Bell Laboratories, the carbon dioxide ($CO_2$) laser is arguably the most widely used laser in medicine. Design improvements over a number of generations have made it the sophisticated and flexible system that is used today in a broad range of dermatological applications. High-voltage electricity or radiofrequency in more recent models is passed through a tube containing the lasing medium - a mixture of $CO_2$ and nitrogen gas to excite $CO_2$ atoms; these are raised to higher energy states that enable first achievement of spontaneous and subsequently of stimulated emission of photons with a wavelength of 10,600 nm. Since this wavelength is in the mid-infrared (i.e. invisible) range of the electromagnetic spectrum, a waveguide a low energy He-Ne laser beam is required to aim the beam. Power ranges between 15-100 W; the chromophore is water: light energy from $CO_2$ laser is adsorbed by intracellular and extracellular water, resulting in coagulative necrosis and skin vaporization [1-3]. The depth of penetration can be changed by altering the laser fluence and/or pulse duration. An exposure time of 0.2 sec and a spot size (i.e. beam diameter) of 0.1 mm are associated with a depth of penetration in the skin of 1 mm. The beam is aimed at the target via a mirror system, an articulated arm, and a focal lens. Originally developed for Continuous-Wave (CW) emission, the $CO_2$ laser can now operate in pulsed mode with different pulse durations (100ms, 250ms and 1ms). Clinical applications depend on pulse duration and range from vaporization of dermo-epidermal lesions to skin resurfacing, which is usually performed with super pulsed and ultrapulsed $CO_2$ lasers. Local or general anesthesia is often required. Beam exposure produces a residual thermal damage that is greater with CW emission (600m below the vaporized layer), but is limited (< 100m) with pulsed operation and pulse durations between 250ms-1ms. The $CO_2$ laser, whether with CW or with pulsed emission, is employed almost exclusively in dermatology.

## Dermatological Surgery

In dermatological surgery the $CO_2$ laser serves a variety of purposes, from tissue excision, replacing scalpels or electro-surgical scalpels, to its destruction by vaporization or coagulation [4].

For tissue excision spot size is very small (a few mm) and power is 12-30W. CW emission generates temperatures exceeding 300°C in the impact zone, resulting in irreversible damage

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and charring in surrounding tissue over at least 100-200m. To minimize the thermal damage, pulsed emission has been adopted in several $CO_2$ lasers, the most advanced of which are characterized by pulses lasting less than 1ms (0.1-0.9ms) and a spot diameter not exceeding 0.8mm. These operational features limit the residual thermal damage to a thickness of 60-100m while still providing coagulation of blood vessels up to 500m in diameter. The main advantage of this $CO_2$ laser is intraoperative hemostasis; it is therefore indicated for a broad range of applications, including treatment of hemorrhagic diathesis of pathological or iatrogenic origin; lesions lying in particularly vascularized areas or at sites not easily accessed with a scalpel; and cases when an electrocoagulator is contraindicated (pacemaker carriers) or the hemostatic effect offers technical advantages, as in laser-assisted eyelid surgery.

The $CO_2$ laser is used even more widely for tissue ablation, both with CW and with pulsed operation [5]. Settings in this case include a defocused spot (2-5mm) and low irradiance (200-500W/$cm^2$), which result in the beam energy being absorbed in a relatively thin tissue layer and in tissue destruction through vaporization and coagulative necrosis. Assuming constant irradiance and spot width, impulse duration is clearly the key factor determining the severity and depth of tissue damage. The amount of tissue destruction can therefore be precisely predicted with super pulsed apparatuses, whereas in CW and shuttered devices it is heavily dependent on operator skills.

Multiple passes may be needed to achieve complete removal of a lesion. The technique is fairly complex, requiring adequate training if only the desired amount of tissue is to be removed. Local anesthesia is commonly administered, even though the more modern pulsed $CO_2$ lasers make it possible to do without in the case of small lesions. The loss of substance heals by second intention; properly performed treatment results in a cosmetically acceptable scar. Laser ablation is used to treat a variety of conditions but it is the first-choice treatment, or at least an effective option, only for some of them. For example, it can be considered as the first-choice treatment for benign pedunculated lesions. Figure 1 shows a seborrheic keratotic lesion in a 61-year-old woman. The procedure was performed with a combined continuous / pulsed mode (spot size 200µm, irradiance 6W); the beam was directed at the junction between the lesion and normal tissue; finally the laser was defocused and "painted" over the wound to control bleeding. This method enables the lesion to be sent for pathological examination. Other indications include removal of dermal nevi at anatomical sites where surgical sutures may induce scarring, resulting in a condition that may be worse than the original appearance of the lesion, and correction of advanced rhinophyma (Figure 2). $CO_2$ laser vaporization can be used to treat benign lesions such as xanthelasma palpebrarum. Though associated neither with functional loss of vision or with the risk of neoplastic changes, surgical removal of these lesions is fraught with problems, principally scarring and pigmentary changes. The $CO_2$ laser is ideal because of its precision and the self-limiting vaporization, due to the high water absorption.

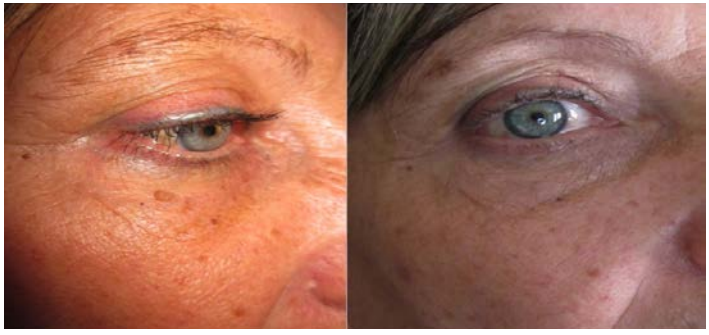

**Figure 1:** Seborrheic keratotic lesion before and 60 days after ablative $CO_2$ laser treatment.

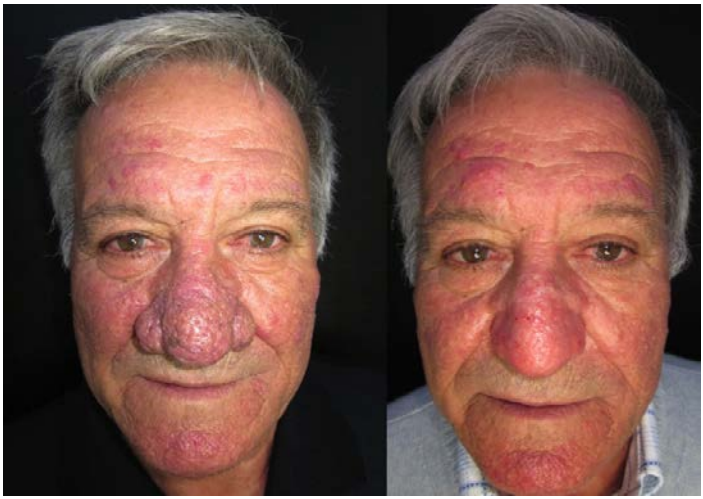

**Figure 2:** Rhinophyma before and 60 days after ablative $CO_2$ laser treatment.

Laser treatment is generally preferred to traditional surgery

i) When excision and suture is not indicated;

ii) When excision would result in healing by second intention; and/or

iii) When bleeding must be minimized; in fact laser treatment enables highly selective targeting of diseased tissue while simultaneously coagulating a considerable portion of vessels.

In all other cases it does not offer appreciable advantages over traditional methods. Although laser ablation is considered a safe procedure, it may entail complications. Formation of keloids or hypertrophic scars, albeit rare, is the most common and severe side effect; pyogenic granuloma, exuberant granulation tissue and bacterial infection at the site of the substance loss are even less frequent [6].

Moreover, in recent years some new/off-label indications of $CO_2$ laser have been reported, including actinic cheilitis, dermatochalasis, silicone granuloma, dyschromia [7], matricectomies, Favre-Raucochot syndrome [8], striae distensae [9], onychomicosis [10] with variable results.

## $CO_2$ Laser Full Ablative Resurfacing

This technique has been ushered in by laser sources delivering very brief pulses (250-900ms) and sufficient fluence (>5J/cm$^2$) to induce vaporization of the epidermis [11,12]. An advance that has made it even more reliable was the development of ad hoc scanners; these provide for beam distribution without overlap, ensuring dose uniformity and effect predictability. Microprocessor-controlled scanners now enable even CW $CO_2$ lasers to be used for skin resurfacing by passing the beam automatically, quickly and precisely over the area to be treated. The procedure is mainly employed to treat photoaging and achieves uniform removal of skin layers to a predetermined depth while inducing a residual thermal damage that ensures minimal scarring. Pulsed and scanned $CO_2$ lasers (fluence 400-500mJ, spot size 125mm-3mm) are the most widely used devices for full ablative resurfacing; the excellent results of the procedure have led to positing an intermediate role for it between peeling (chemical or physical) and surgical lifting.

$CO_2$ laser resurfacing involves pulse durations of less than 1ms corresponding to the thermal relaxation time of a tissue thickness of 20-40m which absorbs the 10,600nm wavelength and a fluence exceeding $5J/cm^2$. In these conditions each pulse can vaporize 20-50m of tissue, removing the epidermis and part of the papillary dermis in a single pass. The residual thermal damage, which extends to a depth of about 50-100m, also provides for effective hemostasis as well as contraction of dermal collagen. $CO_2$ laser resurfacing is therefore indicated when treatment must involve both the epidermis and the superficial dermis (superficial and deep rhytides of the perioral or periorbital region, forehead, glabella, atrophic scars on the face, actinic cheilitis, diffuse facial pigmentation) [13-15]. The mechanism by which laser resurfacing attenuates the photoaging damage and depressed acne scars is not completely clear; however besides epidermis vaporization, well-documented reports suggest a critical role for the contraction of dermal collagen due to the residual thermal damage and to synthesis of new collagen between the newly formed epidermis and the residual dermis.

Despite the availability of scanned lasers full ablative resurfacing is a demanding procedure that requires ad hoc training. Emission settings and pass number must be adjusted to the characteristics of the lesion, e.g. extent, anatomical site, depth of the rhytides, thickness of the actinic keratosis lesions. Moreover, treatment of the eyelids must be gentler compared with the forehead and lips; Fitzpatrick skin types I and II respond better than higher types due to a high risk of Post-Inflammatory Hyperpigmentation (PIH) or depigmentation; and different treatment modalities are applied to small and large areas. Areas such as the perioral region respond very well unlike for instance the hand dorsum; moreover treatment efficacy is directly related to operator skills in interpreting the effects of irradiation on tissue.

Full ablative resurfacing requires anesthesia: local anesthesia by infiltration or nerve trunk block when small skin areas are involved, and general anesthesia or profound sedation for full face resurfacing. The skin should be prepared prior to the procedure, for instance with topical retinoids or bleaching agents, and prophylactic measures adopted in some cases to minimize the risk of postoperative complications [16,17], e.g. by prescribing antibiotics or oral antivirals to subjects prone to Herpes simplex virus infection. Major limitations of the procedure include an extended postoperative period due to slow regression of the erythema and edema, which lasts for months in the case of the $CO_2$ laser; postoperative care to achieve healing of bleeding areas; and practical problems such as delayed return to work, social and recreational activities (sun exposure is not permitted for several months after $CO_2$ laser treatment). Postoperative erythema and edema are generally treated by appropriate head positioning and ice masks, but the more severe cases may require a short course of oral corticosteroids. The use of sunscreens is mandatory for at least 2 months after treatment. Re-epithelization can be promoted by “open” or “closed” techniques: the former consist of frequent application of thick layers of ointments on the de-epithelized area, the latter of semi-occlusive dressings. Open methods afford continuous monitoring of the repair process through easy access to the wound; the advantages of closed methods are postoperative pain control and uncomplicated management by patients. Other recently reported method to reduce the post-operatory complications which include the use of autologous platelet-rich plasma [18] or the conditioned-medium of ADSCs [19].

Despite being the most effective current treatment for photo-aged skin, the risks and side effects associated with laser resurfacing often lead prospective patients to choose more conservative methods. To address these problems new ablative skin resurfacing protocols have recently been proposed that though achieving less significant clinical improvement of rhytides and cutaneous scars involve fewer side effects and a shorter postoperative course.

Single-pass $CO_2$ laser treatments and modulated laser systems seems to offer interesting prospects in this field of cosmetic surgery. The single-pass technique involves a single exposure; the thin layer of damaged tissue is left in situ as a sort of biological dressing. Some reports suggest that, provided that a few standard conditions are met, the procedure achieves ablation of the whole epidermis and stimulates new collagen synthesis and may thus help treat several skin conditions such as hyperpigmentation, limited and superficial elastotic areas, and fine rhytides [20]. Clearly, the results of such new techniques do not compare to those of traditional multipass $CO_2$ laser resurfacing; however, they seem to offer non-negligible advantages in subjects with dark skin (skin type IV to VI), because the less pronounced adverse reactions (e.g. erythema and PIH) are associated with greater safety and predictability of the cosmetic result.

## $CO_2$ Laser Fractional Ablative Resurfacing

Despite the unsurpassed effectiveness of laser resurfacing in treating photodamaged skin the associated risks and side effects have prompted the development, by industry and clinicians, of alternative resurfacing techniques.

Fractional Photothermolysis (FP), introduced by Manstein and colleagues [21] in 2004, is among the most exciting technological discoveries in laser resurfacing in the last two decades. Their original prototype emitted light in a pixelated pattern, producing microscopic columns of thermal injury without ablation (non-ablative FP) whereas ablative skin resurfacing induces a single, confluent, uniform patch of epidermal and dermal injury. Sparing of normal tissue around such microthermal zones results in significantly faster re-epithelization. The tissue injuries created by FP stimulate collagen remodeling and deposition and promote elastic fiber formation. These molecular changes are held to be responsible for the good results of FP. In the newer apparatuses operating parameters can be customized to produce different 3D columns of injury of varied shapes and depths.

In 2007 Hantash and colleagues [22] tested a novel ablative FP device – the fractionated $CO_2$ laser - *in vivo*. The apparatus induced a column of thermal coagulation similar to the non-ablative FP device of Manstein and colleagues [21], with the critical difference that it produced a confluent column of ablation and the thermal injury extended from the stratum corneum through the dermis. Immunohistochemical studies documented that the wound remodeling process lasted at least 3 months, suggesting that greater clinical improvement in skin texture and wrinkling may be achieved with Ablative FP (AFP) than with FP. Computer control provides for varying ablation/coagulation depths without having to change fluence (through pulse stacking on the same point), the space between points, or the mode of emission in the area being treated. AFP involves a very low risk of side effects (PIH, prolonged erythema and edema, scarring) even in dark skin types and a much shorter down-time period compared with full ablative resurfacing. However, though very rare, other side-effects have been reported after fractional $CO_2$ treatment (i.e., acneiform eruption, bacterial infection, yeast infection, contact dermatitis) [23-25].

It has also proved effective in treating moderate to severe acne scarring in terms of clinical improvement and scar volume reduction and in reducing skin surface and texture abnormalities, including moderate to severe rhytides and skin laxity in face, neck, and chest (Figure 3). The extent of results is clearly a function of irradiance: the more it approaches that of the full ablative technique the better. However, the excitement of the initial reports describing skin tightening similar to that obtained with traditional full ablative $CO_2$ resurfacing achieved with only 7-14 days of down-time and a reduced risk of permanent scarring and depigmentation has now abated.

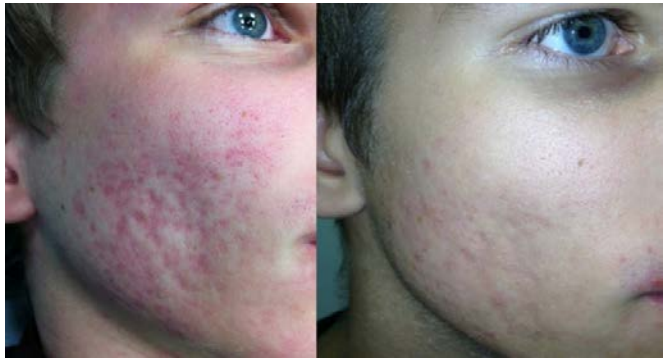

**Figure 3:** Acne scars before and 90 days after fractional $CO_2$ laser treatment.

The more modern devices deliver different modes of energy emission to the same treatment area, to obtain simultaneously deep dermal stimulation and ablation of epidermal lesions. Some protocols have been proposed that involve a multi pass technique using a single device or different tools, to treat different skin depths. New apparatuses that combine the 10,600nm wavelength with other technologies such as radiofrequency or other laser wavelengths (e.g. 1540nm) seem to provide enhanced dermal remodeling. Such new devices aim to maximize outcomes while minimizing the down-time period. Unlike the full ablative technique, fractional $CO_2$ resurfacing rarely requires general anesthesia or sedation, since air-cooling or topical anesthesia are sufficient in most cases. Local or nerve trunk anesthesia may sometimes be necessary, especially when treating the perioral and periorbital areas. A map of the patient's skin should be drawn up to plan treatment of the different areas with different fluence. Fluence in the periorbital area should be 30% lower than in the rest of the face, whereas marked skin damage in the perioral region should be treated with 10-30% increased fluence. Treated areas should be connected to untreated skin by gradually decreasing fluence in the intervening area. The entire face should be treated in each session, maybe using a lower fluence if aging is not marked; this will provide a more uniform skin texture. Multiple sessions are allowed as long as they are spaced at least 90 days apart (Figure 4). $CO_2$ fractional resurfacing can also be combined with surgical procedures such as eyelid surgery or face lifting, to improve skin texture, and affords excellent results in a single session.

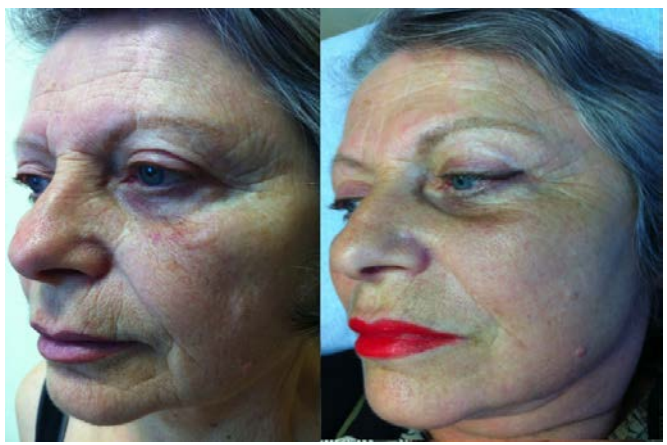

**Figure 4:** Photoaging before and 90 days after fractional $CO_2$ laser treatment.

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