Chemical peeling for acne and melasma: current knowledge and innovations

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ABSTRACT

The skin is a dynamic organ that continuously eliminates an infinite number of keratinized cells through physiological mechanism. Chemical peeling is a widely used cosmetic procedure in medical practice. This technique consists of the application of one or more chemical ablative agents to the skin's surface in order to induce keratolysis or keratocoagulation. Exfoliation is followed by skin and epidermal regeneration from the adjacent epithelium and skin adnexa. Moreover, through an inflammatory reaction and the activation of the inflammation mediators, an increase in fibroblastic synthesis and in the production of new collagen and glycosaminoglycan fibers is induced. After the first treatment session, the appearance and the texture of the skin are significantly improved. Peeling agents may be divided into superficial (epidermis-papillary dermis), medium-depth (papillary to upper reticular dermis) and deep subtypes based on the depth of their penetration (mid-reticular dermis). Superficial peel is mainly used for dyschromia, acne, post-inflammatory hyperpigmentation, melasma and actinic keratosis. Medium depth peel mainly treats solar keratosis or lentigines, pigmentary disorders and superficial scars. Skin photo-ageing, deep scars or wrinkles and precancerous skin lesions require a deep chemical peeling. The aim of this article is to review recent advances in chemical peel of melasma and acne.

KEY WORDS: Chemexfoliation; Acne vulgaris; Melanosis.

Chemical peels promote skin regeneration and remodeling of tissues through the application of exfoliative agents and the most common uses are for acne and melasma treatment. This procedure has been known since ancient time, but in recent years there have been important innovations. For example, trichloroacetic acid (TCA) was historically the gold standard for acne treatment, but recently a new application of TCA has been proposed: at high concentrations (50-100%) has proven successful in the treatment of atrophic acne scars.[1, 2]

In addition to TCA, other types of substances can be used, such as salicylic, lactic, glycolic, mandelic, pyruvic and kojic acid. Another common chemical substance for skin treatment is hydroquinone; it is widely used in chemical peel for melasma treatment but, recently, tranexamic acid (TA) has been proposed as a new treatment option for this disease. TA has anti-plasmin activity, inhibiting melanogenic and angiogenic plasmin properties and is an effective and safe method, especially for phototypes II and III.[3]

The purpose of this review is to summarize the various therapeutic strategies of peeling in the treatment of acne and melasma, analyzing the chemical novelties that can be used for these diseases.

Current chemical therapies for the treatment of acne vulgaris

Acne vulgaris is one of the most frequent inflammatory skin diseases, characterized by an inflammatory process of the follicles and pilosebaceous apparatus caused by several factors such as hyperkeratinization and occlusion of the pilosebaceous follicle, pro-inflammatory activity supported by Propionibacterium acnes (PA) and the release of inflammatory mediators. Acne is characterized by

a remarkable eruptive and evolutionary polymorphism: comedones, pustules, nodules, papules, cysts, which might result in permanent scars. Acne vulgaris mainly involves adolescents and young age groups. Several therapeutic options are available, both topical and systemic, depending on the stage of acne (mild, intermediate or severe). Chemical peeling is an innovative and alternative treatment for acne, there are various chemical agents with different mechanisms of action depending on the depth of action and are commonly classified as superficial, medium and deep peel.[1] The most used agents for acne treatment are salicylic acid (SA), glycolic acid (GA), lactic acid (LA), mandelic acid (MA), pyruvic acid (PA), trichloroacetic acid (TCA), Jessner's solution and kojic acid (KA).

Salicylic acid

Salicylic acid (SA; 2-hydroxybenzoic acid) is a beta-hydroxy acid derived from the enzymatic hydrolysis of salicin, glucoside extracted from the *Salix alba* plant. It is used for superficial peeling due to its strong keratolytic and comedolytic properties.[4] It destroys intercellular lipids that are covalently linked to the cornified envelope surrounding cornified keratinocytes. This leads to the desquamation of the stratum corneum and the activation of basal keratinocytes and fibroblasts.[5] At variable concentrations of 0.5-5% a sebum-normalizing, keratoplasty and antibacterial activity prevails; in concentrations of 10–30% a keratolytic activity predominates. It is applied to the skin for 3-5 min, causing a temporary burning sensation. Evaporation of the solvent leaves a white precipitate in the place of application, indicating the occurred cutaneous precipitation of the acid.[5] This phenomenon is often mistaken with frosting, but salicylic acid peels do not induce a frosting pattern or need neutralisation.[5] They also have a theoretical risk of salicylism if they are applied to large surface areas at one time.[5, 6] Salicylic acid peels are mainly used in comedonal and inflammatory acne and for oily skin.[5] A few applications are adequate for a clear improvement. After a few days of treatment occurs exfoliation and dryness, and re-epithelialization is complete within 7 to 10 days (Figure 1).[7]

Glycolic acid

Glycolic acid (GA) is the most common alpha hydroxy acids (AHA) peeling agent, derived from sugar cane. It is available as an esterified, buffered, partially neutralized or free acid solution.[8] Concentrations ranging from 20% to 50% are used for superficial peeling, instead with higher concentrations (70%) entering the medium-depth category.[7] This acid is non-self-neutralizing, so careful application and observation of time and clinical signs (*e.g.* erythema and frosting) are required.[7] In case of adverse reactions it is necessary to apply an alkaline neutralizing agent such as sodium bicarbonate neutralization.[7] Furthermore, glycolic acid in combination with lightening agents, like kojic acid, allows the treatment of superficial skin hyperpigmentation. Chemical peels can be made with a solution of glycolic acid, applied for 3-5 minutes. The number and frequency of applications depends on the intensity and severity of the clinical picture, usually repeated once every 15 days for 4-6 months until the desired clinical result is achieved.[8] Re-epithelialization is complete within 7 to 10 days, after several days of exfoliation (Figure 2).[7]

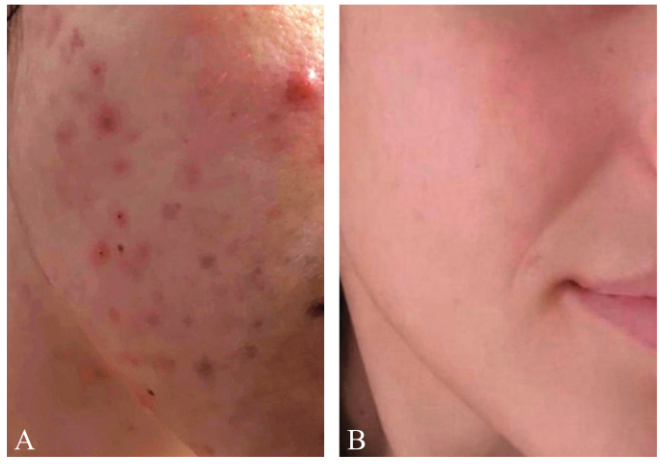

Figure 1. In this 22-year-old patient, four cycles of superficial salicylic acid peeling were performed to reduce seborrhea (A), counteract the formation of new comedones and reduce the formation of blackheads. Each peeling has been performed every month for four months with an improvement in the texture of the skin and a reduction in the number of blackheads (B).

Lactic acid

Lactic acid (LA), which is structurally similar to GA except for an additional methyl group at the β-carbon end, has a lower pH than glycolic acid at same concentrations, permitting an efficient chemexfoliation at lower concentrations.[7] It is used for superficial peeling either alone or in combination with other peels. LA reduces the layers of the stratum corneum by decreasing corneocyte adhesion and eliminate the dead skin cells.[2] LA is also used for the treatment of photodamage and superficial hyperpigmentation. Neutralization is necessary and over several days of exfoliation, re-epithelialization is complete within 7 to 10 days.

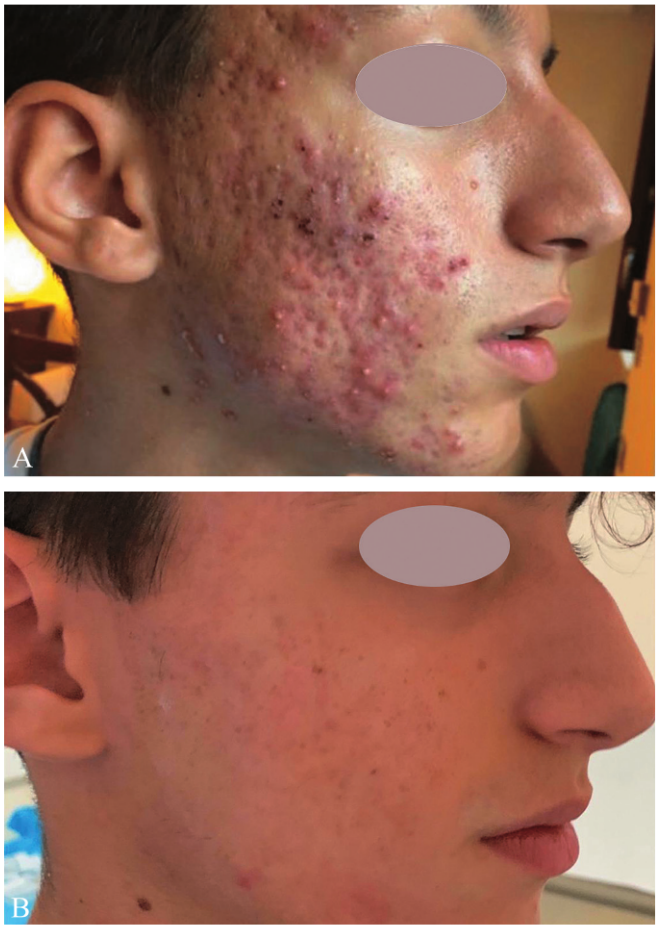

Figure 2.—A) In this 16-year-old subject, multiple treatments were performed to achieve this result. First the patient was treated with oral isotretinoin for four months, after which a total of eight peelings were performed, four based on glycolic acid and four based on salicylic acid; with this protocol, the aim was to reduce seborrhea, prevent the formation of new papules or pustules, reduce post-acne scars and improve the texture of the skin. B) Result of the treatment at 1 year.

Mandelic acid

Mandelic acid (MA), a phenolic alpha-hydroxy acid, is an aromatic glycolic acid with a benzene ring connected to the alpha-carbon where the hydroxyl group is attached.[7] It is widely used for the treatment of mild to moderate acne.[1] In addition to acne, its use is also recommended for the treatment of superficial erythema and dyspigmentation.[7] Equally to other α-hydroxy acids, MA causes exfoliation of epidermis by reducing corneocyte adhesion.[1] MA is better tolerated on the skin and is often used as alternative to GA peel. MA peel is formulated in a combination peel with SA (20% SA, 10% MA).[9] There may be a minimal desquamation, and re-epithelialization is complete within 3 to 5 days.

Pyruvic acid

Pyruvic acid (PA) is an a-keto acid that differs from AHA by having a carbonyl group in the position of a carboxyl group.[10] PA is physiologically converted to lactic acid and is used in concentrations of 40-70%.[5] It causes ablation of the stratum corneum and dermo-epidermal separation leading to decreased epidermal thickness.[10] PA peels have demonstrated efficacy in the treatment of acne vulgaris and disorders of excess sebum production, as well as mild photoaging and superficial hyperpigmentation.[11] It is also commonly used for superficial peeling to treat inflammatory and comedonal acne. This acid is not self-neutralizing and it should be neutralized with an alkaline solution. Over several days of treatment occurs exfoliation, and re-epithelialization is complete within 5 to 10 days.

Trichloroacetic acid

Trichloroacetic acid (TCA), a trichlorinated carbonic acid, is a medium-depth peeling agents. TCA causes denaturation of epidermal and dermal proteins, destruction of dermal collagen, and coagulative necrosis of epidermal cells. This peel self-neutralizes. Its indication is mainly for the treatment of acne, actinic photo-damage, hyperpigmentation, actinic keratoses and also for acne scars.[7] TCA used at higher concentrations has a high risk of complications, including dyschromia, scarring, and bacterial superinfection. Usually, it is used at concentrations of 35% to 50%, with or without adjuvant combination products. An important phenomenon caused by TCA is frosting, the whitening of the skin due to protein coagulation.[11] After treatment with medium-depth peels, the erythema initially intensifies, with a peak 4 to 5 days post-treatment. Exfoliation is complete within 10 to 14 days.[7]

Kojic acid

Kojic acid (KA) is produced by certain fungi and it is a copper chelating agent also known as 5-hydoxyl 2-(hydroxymethyl)-4-pyrone. Its lightening properties are linked to the inhibition of the tyrosinase enzyme. It is used at 1-4% concentrations and commonly in combination with GA or other lightening agents (arbutin, aloesin, soy extract, etc.) to increase penetration and efficacy.[1] KA is primarily used to treat skin pigmentary disorders and in patients with active acne, to prevent and cure post-inflammatory hyperpigmentation.

Jessner's solution

Jessner's solution (JS) is a superficial peeling used as a therapeutic adjuvant for acne and is obtained by combin-

ing 14% SA, 14% resorcinol and 14% LA in 95% ethanol. Its function is to increase the penetration of other peelings by breaking the bridges between the keratinocytes. The resorcin is a 1,3-dihydroxybenzene that results in the breakage of the hydrogen bonds of the keratin through a process of keratolysis and cell death through the rupture of the cell membrane, and it is also a powerful bactericide.[1]

Current chemical therapies for the treatment of melasma

Melasma is an acquired pigmentary skin disorder, characterized by symmetrical asymptomatic hyperpigmentation, with reddish-brown or blue-grey macules or patches located mainly in the photo-exposed areas and especially the face.[12] The most affected areas are the cheekbones, nose, forehead, chin and upper lip. The neck, extensor arms and upper back are localizations associated with menopause.[12] It is often observed in women and individuals with Fitzpatrick skin types IV through VI. The pathogenesis of melasma is complex and multifactorial: genetic predisposition, intense ultraviolet radiation exposure, and hormonal influences such as pregnancy, hormonal therapies, and oral contraceptive pills are implicated. The treatment of melasma requires a multimodality approach, including the use of hydroquinone, azelaic acid, kojic acid, glycolic acid and salicylic acid. Of these, hydroquinone remains the gold standard.

Priming in the melasma is mandatory for at least 4 weeks before the procedure. The most commonly used product is 4% hydroquinone, in addition to this can be used glycolic acid 6-12%, retinoids alone or in combination with kojic acid. This procedure ensures more uniform penetration of the reagent and also reduces the risk of complications.

Broad spectrum sun protection (SPF 50+) is necessary and, if not yet used, should be initiated at the first consultation.

Hydroquinone

Hydroquinone is the most potent inhibitor of the enzyme tyrosinase, which regulates the rate step of melanin production and represents the gold standard for melasma treatments, particularly of the epidermal type. HQ preparations are a concentration of 2-5% and are applied once a day, for at least 3 months up to one year. The depigmenting effects of HQ treatment become evident after 5-6 weeks. HQ creams also contain other agents, such as sunscreens, retinoids and glycolic acid.[2] Also, it can inhibit DNA and RNA synthesis reversibly and may also affect the production of melanosome, an organelle found in animal cells, the site for synthesis, storage and transport of melanin. Unfortunately, topical preparations based on hydroquinone can cause side effects such as erythema, burning, photosensitivity, and, in more serious cases, ochronosis.

Azelaic acid

Azelaic acid is a fatty acid with a disinfectant and antimelanin action, making the face more homogeneous and uniform in color. Therefore, it is effective for patients with very dark skin, suffering from melasma. The mechanism of action is similar to that of HQ, but, unlike HQ, azelaic acid acts alone on hyperactive melanocytes, sparing areas with functioning melanocytes.

Recently, a new procedure has been proposed which consists of using azelaic acid in combination with resorcinol and phytic acid (20% azelaic acid + 10% resorcinol + 6% phytic acid). Satisfactory results have been obtained with reduced complications and side effects compared to the use of glycolic acid 50%.[13] Azelaic acid is formulated as a 20% cream and has proved to be a valid alternative to hydroquinone. The primary adverse effect is skin irritation, but no phototoxic or photoallergic reactions have been reported.

Kojic acid

KA is an important inhibitor of tyrosinase: it shows a competitive inhibitory effect on the monophenolase activity and a mixed inhibitory effect on the diphenolase activity of tyrosinase. Regurarly KA is formulated in creams, but it is also possible to find it in the form of lotions, gels or serums at rather low concentrations to minimize the risk of skin side effects (allergies, skin sensitization, dermatitis, itch). It is commonly used in combination with exfoliating agents, like MA and SA.[14]

Glycolic acid

GA falls into the category of superficial peeling that causes a slight exfoliation; if properly used it allows a clear rejuvenation of the skin without causing scabs, burns or redness.[8] For melasma peeling, it is used in a concentration of 30-70%. In lotion or gel, the solution is brushed on well cleansed skin and kept on the skin for 1 to 5 minutes depending on concentration and individual sensitivity. Weekly treatments are required after two or three weeks for a series of 4-6 sessions. When the skin begins to redden, dab it with a solution of water and bicarbonate that blocks the action of the acid and rinses the face

abundantly. To maintain the results obtained, a glycolic based cream with a concentration of between 8% and 15% is applied between each peel. Although gel-based peel is preferred for sensitive skin, aqueous solution has higher bioavailability of free acid and it is preferred over gel-based peels for cosmetic results. GA can be also used in combination with other compounds like hydroquinone, KA, azelaic acid and SA. To increase clinical effectiveness, GA peels are combined with topical therapies such as 10% topical GA, topical vitamin C, azelaic acid or adapalene (Figure 3).[14]

Salicilic acid

SA peels in 20-30% strength help in the elimination of epidermal pigment resulting in an effective treatment in patients with skin dyschromia such as melasma. Thanks to its lipid-solubility, it has a better keratolytic action and a smoother post peel texture. SA is one of the most widely used chemical peelings, whose properties and indications depend on the concentration used (10%, 20%, 30%, 40%, and 50%). This peeling has been found to be safe and well tolerated by all groups of patients and in all skin types (Fitzpatrick I-VI). The possible contraindications to SA peeling are an active dermatitis at the peeling site, infection, tanned skin, acute viral infection and pregnancy.[14]

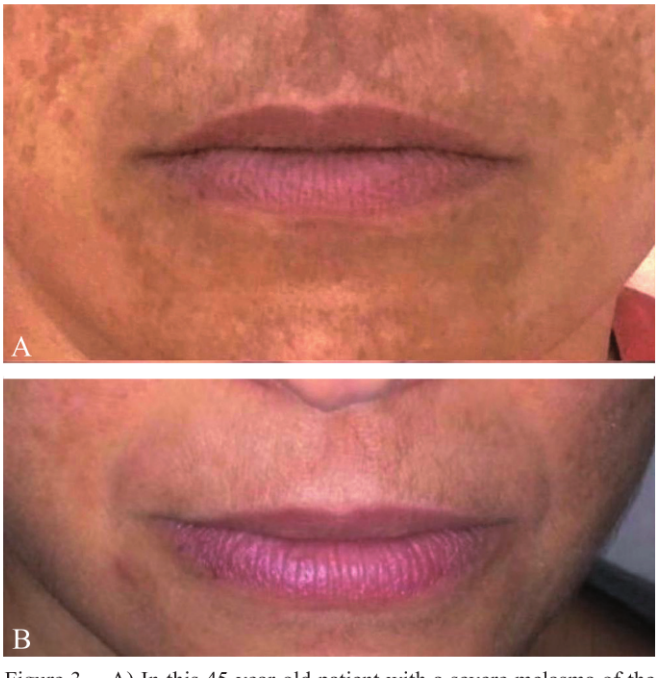

Figure 3.—A) In this 45-year-old patient with a severe melasma of the lip contour, four cycles of exfoliation with kojic acid and glycolic acid were performed; each treatment was performed three weeks apart with an average time of application of about 120 seconds. B) Result of the treatment at 12 weeks.

Q-switched Nd:YAG laser

The Q-switched Nd:YAG laser has achieved excellent results in the treatment of melasma, although several sessions are necessary, and complications may occur especially in darker phototypes.

The literature reports cases treated exclusively with the low-fluence Q-switched Nd:YAG laser and other patients treated with the combination of laser and Jessner's peel. Both methods were effective, but the combined method is preferred, especially in dark skin as it allows for better cosmetic results with fewer side effects as it reduces the number of laser sessions and costs.[15]

What's new in chemical peeling?

Recently, several studies have documented the efficacy of cysteamine, methimazole, flutamide and tranexamic acid in chemical peeling procedures.

Cysteamine hydrochloride (β-mercaptoethylanine hydrochloride) is naturally produced in the human body and is a degradation product of the amino acid L-cysteine. In a randomized, double-blind trial of 50 patients, cysteamine 5% cream showed significant efficacy in the treatment of melasma.[16]

Methimazole is an oral anti-thyroid drug used to treat patients with hyperthyroidism and has been shown to cause depigmentation when applied topically. It has been used in patients with melasma and post inflammatory hyperpigmentation and causes significant skin lightening, due to its powerful effect of peroxidase inhibition which blocks melanin synthesis. Methimazole 5% was applied daily in 20 patients with epidermal melasma and did not induce any significant changes in serum thyroid-stimulating hormone, free thyroxine, and free triiodothyronine levels. Methimazole was well tolerated with minimal cutaneous side effects. However, methimazole can be applied only to areas affected by melasma and should not be used as a general cosmetic lightening agent.[17]

Flutamide is a nonsteroidal antiandrogen that blocks the action of testosterone by binding to the androgen receptor. Seventy-four women were enrolled in a parallel, randomized, 16-week trial that compared once daily flutamide 1% with hydroquinone 4%. Skin hyperpigmentation improved, and the results of MASI and colorimetry scores revealed similar efficacy for flutamide and hydroquinone 4%.[18]

Tranexamic acid (TA) is an anti-fibrinolytic agent and it represents a promising treatment for melasma. TA administered orally (at the dosage of 500 to 1500 mg 2-3 times daily for 1 to 6 months), topically (2%, 3%, 5%), and through physical methods (microinjection or microneedling) acts by the inhibition of UV-induced plasmin activity in keratinocytes.[3] It blocks the binding of plasminogen to keratinocytes, thus decreasing the free arachidonic acid and decreasing the production of prostaglandins, which are known stimulators of the tyrosinase activity. In addition, plasmin is thought to convert matrix vascular endothelial growth factor (VEGF) into freely diffusible forms, leading to angiogenesis. Consequently, in the treatment of melasma, TA can exert its double effect by reducing the production of pro-melanogenic factors and decreasing the erythema and vascularization. The dosage for the treatment of melasma is much lower than when indicated as an anti-fibrinolitic.[3]

Conclusions

Topical and systemic therapies are the cornerstone of the treatment of acne and melasma. The therapeutic options, as an adjuvant and maintenance therapy, available to date for the treatment of acne and melasma are greatly increased.

It should also be noted that the chemical peeling may represent a valid alternative also for all the patients with adverse reaction to "common" topical anti acne therapies.[19]

Peeling has become a very well performed procedure in the US and Europe and the development of increasingly specific substances with reduced side effects increases patient compliance for these treatments. One of the crucial points of the peeling, regardless of the substance used, is the use of priming which should be done for 2-4 weeks before the peeling, the correct disinfection of the skin before the treatment and the application of creams rich in lipids after the treatment. These simple rules make it possible to reduce the risk of infection and speed up the healing of the skin. The clinical and aesthetic results of these treatments are increasingly satisfactory and the research is so promising that in the coming years the peelings could replace even the most modern equipment for photo-rejuvenation; the rapid healing, low invasiveness and low cost will make these treatments the most carried out in aesthetic dermatology. For this reason, a continuous update on the substances that can be used is essential to ensure the best therapeutic option for the patient.

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