Leading article

Chemical peeling – the scientific view

Nanna Y Schürer[1]

Sri Lanka Journal of Dermatology, 2006, **10**, 3-9

Introduction

Facial chemical peeling is defined as the application of one or more exfoliating chemicals to the skin, resulting in destruction of portions of the epidermis or dermis with the resulting regeneration of new epidermal and dermal tissue. Several chemical agents are currently used to perform chemical peeling of the face. These include

1. alpha-hydroxy acids (AHA)
2. salicylic acid (SA)
3. resorcinol
4. pyruvic acid/pyruvate
5. trichloracetic acid (TCA)
6. Jessner's solution (14% lactic acid, 14% resorcinol, and 14% salicylic acid)
7. a combination of 1.-6., and
8. croton oil in phenol.

The depth of wounding produced by chemical peeling depends in part on the strength of the agent employed. Moreover, other factors such as the pH of the peeling solution, its galenic preparation as well as preparation of the skin, skin type, anatomical region to be peeled, peel procedure and post peel procedure will influence the depth of a peel. Classification of chemical peeling has been defined according to the histologic depth of injury exerted by the agent (Table 1).

Table 1. Classification of chemical peeling

Depth	*Injury*	*Chemical*
Superficial	Epidermal	AHA, SA, Jessner
Medium	Papillary to upper reticular dermis	TCA Combination peel
Deep	midreticular	Croton oil in Phenol
		TCA in combination with other peeling substances

The scientific basis (as far as available) for the chemicals employed is discussed as follows for alpha-hydroxy acids (including pyruvic acid), beta-hydroxy acid, trichloracetic acid and phenol and its derivatives (resorcinol).

Alpha-Hydroxy acids (AHAs)

For more than 20 years, alpha-hydroxy acids (AHAs) have been used in dermatology as superficial peeling agents. Most AHAs are naturally occurring compounds, i.e. they occur as metabolites within the human organism as well as in nutrients. While they were originally extracted from various plants, hence the synonym "fruit acids", they are now chemically synthesized. Many AHAs are nontoxic at physiological concentrations. At room temperature they occur as crystalline compounds and they dissolve readily in water. With increased temperature, a H_2O molecule dissociates from the AHA-molecule. AHAs occur as acids, salts or as ionized complexes. As any alcohol, a second OH-group may oxidize to its keto-form. The oxidation is reversible. Hydroxyl- and keto-carbonic acids are partners of cellular redox reactions. AHAs are organic carboxylic acids. Compared to their corresponding non substituted acid, AHAs are more acidic due to the presence of the additional OH-group (Table 2).

Table 2. pKs of organic acid and their corresponding alpha-hydroxy acids

Carbonic acid	*pKs*	*a-Hydroxy acid*	*pKs*
Acetic acid	4,76	Glycolic acid	3,83
Propionic aid	4,88	Lactic acid	3,87
Succinic acid	4,17	Malic acid	3,46
Caprylic acid	4,85	Mandelic acid	3,37
Succinic acid	4,17	Tartaric acid	3,24

The acidic strength of an acid is determind by the proton (H^+-ion) dissociation in solution and is expressed as "pKa". The pKa is the negative common logarithm of the dissociation constant. The pKa-

[1]*Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrück.*
E-mail: nschuere@uos.de.

difference of "1" equals an acid difference of "10". The lower the pKa, the stronger the AHA. For example, glycolic acid (pKa 3.83) is stronger than acetic acid (pKa 4.76). Aqueous solutions of AHAs have different pH values, depending on the acid concentration. The pH of a solution is expressed as the negative common logarithm of the proton (H+-ion) concentration. For example, a glycolic acid solution has a pH of 1.2 at 50% and a pH of 1.7 at a 5% concentration (Table 3).

Table 3. pH for aqueous solutions of glycolic acid

Glycolic acid concentration [%]	*pH*
5	1,7
10	1,6
20	1,5
30	1,4
40	1,3
50	1,2
60	1,0
70	0,6

AHA as peeling agents

Several AHAs have been used for skin rejuvenation:

Glycolic acid (2-hydroxyacetic acid) (GA) is readily soluble in water, less so in ethanol and acetone. It occurs in sugar cane and grapes. Glycolic acid is the smallest molecule of all AHAs. In contrast to the other AHAs glycolic acid does not occur in isomeric forms, because its α-atom binds two "H"-ions. Chemical industries use glycolic acids for chelating Ca^{2+}-ions. Concentrations between 20 and 70% have peeling properties as long as the preparations are not neutralized or buffered. Depending on the concentration, product formulation, degree of neutralization, and presence of buffers the pH changes from 0.08 to 2.75.

Lactic acid (2-hydroxypropanic acid) (LA) is soluble in water and ethanol. It may be extracted from cheese, sour milk, pickled cabbage and cucumbers. Lactic acid results from the fermentation of carbohydrates by streptococci and lactobacilli. Under anaerob conditions lactic acid is a biologic metabolite. Under these conditions muscular cells release L-lactic acid, which may be measured not only in the muscle itself, but also in the blood, kidney and gall bladder tissue. Lactic acid is present in the skin, which contains three times more lactic acid than the blood.

Malic acid (2-hydroxysuccinic acid) is soluble in water and ethanol and is commercially available as a white crystalline compound. Malic acid occurs in apples, pears, grapes, peaches, quinces and gooseberries. In the skin it is a metabolite of the citric acid cycle. Malic acid is a dicarboxylic acid with one OH-group at the α-position of one carboxy group. Malic acid has isomeric forms (D-malic acid, L-malic acid and DL-malic acid) due to the asymmetrical nature of the molecule.

Mandelic acid (phenylglycolic acid) is soluble in water and alcohol and is commercially available as a white crystalline compound. Because of its bactericidal and bacteriostatic effects in an acid environment, mandelic acid has been used as a urinary antiseptic.

Tartaric acid (2, 3-dihydroxysuccinic acid) is soluble in water and ethanol and is commercially available as a white crystalline compound. Tartaric acid is a dicarboxylic acid with two OH-groups at the α-position of one carboxylic group. Owing to the asymmetrical nature of this molecule, tartaric acid has isomeric forms such as D-tartaric acid, L-tartaric acid, DL-tartaric acid and meso-tartaric acid. L-tartaric acid is a natural metabolite in fruits and plants, occuring for example in grapes. Tartaric acid occurs as a salt, i.e. tartar, which precipitates as sugar ferments to alcohol. In contrast to L-tartaric acid, D-tartaric acid is a rare natural metabolite. It has been extracted from the leaves of a westafrican tree "bankia reticulata".

Citric acid (2-OH-1, 2, 3-propantricarbonic acid) is soluble in water and ethanol. Citric acid is a tricarboxylic acid with one OH-group at the α-position of one carboxylic group. At the same time, the OH-group is in β-position to the two remaining COOH-groups. In the literature, citric acid is therefore described as "α-hydroxy acid" or as "β-hydroxy acid", depending on the COOH-group referred to. Citric acid is a synergist for antioxidants, binding metal ions, which accelerate oxidative reactions. Citric acid occurs in citrus fruits (lemons, oranges), pineapples, figs, bananas and berries (strawberries, raspberries, red- and black currant). Lemon juice contains 4.7-7.9% citric acid. In the skin citric acid is a metabolite of the citric acid cycle. The concentration of citric acid in the blood and urine is low.

Gluconic acid (2, 3, 4, 5, 6-pentahydroxyhexaic acid) is readily soluble in water and less in alcohol and ether. D-Gluconic acid is a metabolite of microbial glucose oxidation, and is therefore found in the skin.

Pyruvic acid, an alpha-keto-acid, has been recently used as a medium chemical peeling agent in subjects with inflammatory acne, moderate acne scars, greasy skin, actinic keratosis, and warts. A clinical evaluation, using 50% pyruvic acid, of the patients demonstrated a smoother texture, less evident fine wrinkles, and evident lightening of hyperpigmentations (freck-

les and lentigines). 50% pyruvic acid peeling can be proposed as a safe and efficient treatment for moderate facial skin aging[1].

AHA as cosmetic ingredient

Legislation

AHAs are capable to produce a significant reversal of both epidermal and dermal markers of photoaging. AHAs are also used to treat epidermal lesions or those in the superficial dermis, including fine wrinkles, actinic keratoses, melasma, lentigines, seborrhoic keratoses. Therefore, AHAs may not be pure cosmetic ingredients. In the US concentration of 1 – 8% of glycolic acid are in the market without any prescription. Higher concentrations are under medical supervision. In Europe no legislation exists with respect to the use of AHAs. Only in Switzerland a maximal concentration of 10% AHA with a minimal pH of 3.5 has been defined for cosmetic use.

Homecare products containing AHAs may be – buffered or neutralized – formulated as a solution, lotion, creame, ointment or gel. Epidermal efficacy of these formulations is low, because the stratum corneum is an effective barrier to most molecules or ions with negligible lipid solubility. For example, sodium glycolate has an ionic structure. In aqueous environment sodium glycolate dissociates into sodium ions and glycolate. These ions and molecules may not readily penetrate the stratum corneum of the skin. However, dermal efficacy as demonstrated by Ditre et al, may indeed lead to changes in collagen structure over a treatment period of several months. Possibly, AHAs penetrate through the hair follicle to readily enter the deeper structures of the skin.

Formulations low in pH may irritate sensitive skin upon repeated application disturbing the physiological pH between 4.2 and 5.6. Lower concentrations or partially neutralized, buffered AHAs are present in creams and lotions. Claims on improving skin surface appearance and rejuvenation properties have lead to more than 160 new cosmetic products in 1994 alone. Despite the extensive use of AHAs in cosmetic products and peeling procedures, their mechanisms of action are not well understood. Several hypotheses have been proposed; scientific proof is missing. However, the literature reveals some interesting studies:

Human and animal studies

A placebo controlled study on 17 volunteers applying a lotion containing either 25% glycolic, lactic, or citric acid (pH 3.5) to one forearm and a placebo lotion to the opposite forearm for an average of 6 months was one of the first histologic and ultrastructural studies performed. AHAs caused an approximate 25% increase in skin thickness. The epidermis was thicker and papillary dermal changes included increased acid mucopolysaccharides, improved quality of elastic fibers, and increased density of collagen[2]. Increase of skin firmness and thickness was studied using either 5% or 12% LA test solutions (pH 2.8) twice daily over a time period of 16 weeks. Treatment with 12% LA resulted in significant epidermal and dermal effects[3].

A study on the effect of GA at various concentrations and pH levels was performed on 20 volunteers applying formulations with varying amounts of GA at different pH levels (3.25, 3.8 and 4.4)[4]. All pH levels at all GA concentrations resulted in a normalization of ichthyotic/xerotic skin. Collagen deposition increased and was more effective using products with higher GA concentration (13%) at a pH of 3.8 to 4.0. Other studies confirmed the dermal effect of AHAs[5]. Comparing the effect of 20% citric acid lotion to vehicle alone on skin thickness, viable epidermal thickness, and dermal glycosaminoglycan content, image analysis of biopsy sections revealed increases in viable epidermal thickness and dermal glycosaminoglycans in treated skin. Topical citric acid produced changes similar to those observed in response to GA, ammonium lactate, and retinoic acid including increases in epidermal and dermal glycosaminoglycans and viable epidermal thickness[5].

Studies on normal human skin (11 subjects), comparing daily AHA application (GA, lactic acid (LA), tartaric acid (TA) and gluconolactone (GLU) 8% cream base) to vehicle alone over 4 weeks revealed no increase in TEWL, even after application of a patch test using 5% SLS on the volar arm[6]. Also, GLU showed a barrier protecting effect, reflected by lower TEWL values. Repeated application of AHAs may stimulate ceramide biosynthesis leading to increased formation of SC intercorneocyte lamellar structures and reduce irritation by sodium lauryl sulfate. Some AHAs for cosmetic use therefore seem to induce barrier restoration. The effects of AHAs on the stratum corneum include normalization of SC exfoliation by reducing intercorneocyte cohesion, resulting in an increased plasticization and a decrease in dry scales[6].

The effects of 5% GA or LA preparation (pH 3.8) on the skin barrier of hairless mice was investigated and compared to vehicle alone. There were no changes in TEWL, capacitance or epidermal thickness. Normal lipid layers of the SC and calcium gradient were demonstrated. However, on electron microscopy AHA-treated normal epidermis showed an increase in the secretion of lamellar bodies and a decrease in the number of SC layers in comparison to vehicle treated epidermis[7].

Studies performed by Fartasch et al. revealed no changes in the LB secretory system employing electron

microscopy[8]. Enhanced desmo-somal breakdown was observed after 3 weeks of treatment with a 4% GA formulation compared to vehicle-treated samples. TEWL values remained unchanged.

Oral or dermal pharmaco-toxicological studies have not been published. GA has a smaller molecular size and is water-soluble. It can penetrate the skin, diffuse and move into the deeper epidermal layers. More placebo controlled, double blind, clinical studies are required to substantiate the claims and to evaluate the safety of GA.

A randomized, placebo controlled, double blind study was performed comparing 10% GA, 2% 2-hydroxy-5-octanoyl benzoic acid (beta-lipohydroxy acid LHA) and 0.05% all-trans-retinoic acid (RA). Volunteers treated one forearm twice daily with one of the active products and the other one with the vehicle over 2 months. Employing histochemistry and quantitative immunohistochemistry improvement in the various epidermal compartments was the most prominent finding at the RA-treated site. The LHA-treated site also exhibited similar positive changes, however GA showed no significant effect. In the presently tested concentrations and formulations, RA had a beneficial impact upon the aging epidermis[9].

Studies on the incidence of epidermal pre-cancers or cancers

A small placebo controlled double blind study on the use of a 10% GA gel (pH 3.52) versus placebo gel (pH 5.75) was performed on 6 asian and 6 caucasian volunteers, applying the gels on the back and contralateral extensor forearms over 3 weeks after UVA and UVB irradiations. An increase in UV-induced redness and tanning was interpreted as evidence for increased photosensitivity after GA use[10].

To study the functional role of GA on UV-induced skin tumor genesis, a study on hairless mice was performed by application of GA after UVA and UVB irradiation. GA reduced UV-induced skin tumor development: a 20% reduction of skin tumor incidence, a 55% reduction of tumor multiplicity and a 47% decrease in the number of large tumors was observed and accompanied by decreased expression of the following UV-induced cell-cycle regulatory proteins: proliferating cell nuclear antigen (PCNA), cyclin D1, cyclin E, and the associated subunits cyclin-dependent kinase 2 (cdk2) and cdk4. In addition, the expression of p38 kinase, jun N-terminal kinase (JNK), and mitogen-activated protein kinase (MEK) also was lower in UV + glycolic acid-treated skin compared with UV-irradiated skin. Moreover, transcription factors activator protein 1 (AP-1) and nuclear factor kB (NF-kB) activation was significantly lower in UV + GA-treated skin compared with UV-irradiated skin. The decreased expression of the cell-cycle regulatory proteins and signal mediators may play a significant role in the inhibitory effect of GA on UV-induced skin tumor development. In addition, the inhibition of activation of transcription factors AP-1 and NF-kB could contribute significantly to the inhibitory effect of GA[11].

Studies on AHAs as peeling agent

Few studies have been performed on the peeling properties of the mentioned ingredients. A small histologic examination on the use of 50% and 70% GA peels with various pH[12] on two patients revealed no increased desired clinical effect with increased epidermal irritation, such as crusting and necrosis[13]. A further histologic study on hairless mice demonstrated that neither degeneration nor inflammation is required to achieve epidermal and dermal regeneration [14].

Salicylic acid

Salicylic acid (SA), a beta-hydroxy acid has been used for resurfacing moderately photodamaged facial skin. Dermal pharmaco-toxicological studies on the resorption of lipophilic SA have been published. SA easily penetrates the skin[12]. Salicylism following percutaneous application has been documented in the literature, but the event is rare and depends on a number of cofactors, such as age, skin damage, surface area involved, dosage level, renal disease[15].

The absorption of 30% C^{14}-SA in polyethylene glycol was studied in hairless mice[13]. 1 hour after application the plasma concentration of radioactivity was 1665.1 ng eq/ml, significantly lower than the 21437.6 ng eq/ml observed in mice with SLS-damaged skin. Microautoradiograms of intact skin showed that the level of radioactivity in the cornified cell layer was similar at 6 h after application. However, in damaged skin, the overall level of radioactivity showed a decrease by 3 h after application. In the carcasses remaining after the treated intact and damaged skin had been removed, 0.09 and 11.38% of the applied radioactivity remained, respectively. These findings confirm that 30% SA in PEG vehicle is little absorbed through the intact skin of hairless mice, and suggest that salicylism is not likely to occur in humans with intact skin during chemical peeling with this preparation. When the agent is applied topically to mice skin at a dose of 6 g SA, the dose level for human to give comparable plasma concentration (1.65 ug/ml) would be 2000 times higher.

SA (30% in a hydro-ethanolic vehicle) has been compared to GA 70% unbuffered in 5 patients in a half-face model. SA causes significant more desqua-

mation than GA. Pigment spots, decreased surface roughness, and reduction of fine lines was observed[16]. SA serum levels did not reveal concentration levels of salicylate toxicity or even anti-inflammatory levels. Own unpublished data on the direct comparison of SA and GA peels with a comparable pH of 2.0 also revealed significantly more irritation and inflammation on the SA peeled side compared to the GA side. However, the clinical outcome 2 weeks after the procedure was comparable.

To evaluate the effects of chemical peeling with 30% SA in PEG on skin tumor formation, hairless mice were irradiated with UVB for 14 weeks, with or without treatment every 2 weeks with 30% SA in PEG for a total of 18 weeks. The total number of tumors was greatly reduced in the treated vs. control mice, as was skin tumor development. SA in PEG peels as well as GA peels may help to prevent and reduce the number of UVB-induced skin tumors[17]. Reorganization of the epidermis and rebuilding the superficial dermal connective tissue without evidence of inflammatory infiltrates may account for this effect.

Trichloracetic acid

A long lasting facial chemical peel may be achieved with the caustic agent trichloracetic acid (TCA), which has been used for decades to treat extensive actinic keratosis, solar elastosis and wrinkles. TCA destroys the epidermis and upper dermis, causing the denaturated skin to slough within 5-7 days. The sloughed epidermis is replaced within 7 days by new keratinocytes migrating from the cutaneous adnexa. Regeneration of the dermis followed by collagen remodeling occurs within the following 6 months.

Histological changes produced by chemical peeling agents to UVB-irradiated skin of hairless mice was analyzed comparing 30% SA dissolved in macrogol (pH 1.16), 35% TCA dissolved in distilled water (pH 0.65) and 20% GA dissolved in glycerin (pH 1.88). Untreated, irradiated skin served as control revealing irregular epidermal hypertrophy by day 70. All skin specimens treated with chemical peeling agents exhibited a unique connective tissue layer composed of fine collagen fibers beneath the epidermis. 20% GA dissolved in glycerin lead to rebuilding of the epidermis and formation of collagen fibers without the evidence of inflammation. 35% TCA produced severe tissue damage and marked inflammation. No inflammatory infiltrates were seen with 30% salicylic acid in macrogol at 70 days. However, epidermal thickness increased with GA, but decreased with SA[6].

It seems reasonable to think that also TCA might reduce tumorigenesis. To evaluate the effects of 35% TCA on skin tumor formation, hairless mice were irradiated with UVB for 14 weeks. The total number of tumors was greatly increased in the TCA treated vs. the control areas[19].

Croton oil and phenol

Deep peels are characterized by an inflammatory response in the deep reticular dermis, which induces production of new collagen and ground substance. Phenol peels may be performed with various formulations, such as pure phenol (88%) or phenol mixed with soap, water, croton oil, and sometimes olive oil. Historically, the Baker-Gordon formula, with phenol diluted to 50% to 55%, was thought to penetrate deeper than full strength, undiluted phenol. The rationale for this was that full strength phenol presumably caused an immediate coagulation of epidermal keratin proteins and thus formed a barrier to further penetration. Moreover, the liquid soap Septisol was thought to act as a surfactant that reduces skin tension, allowing for more even penetration of phenol, while Croton oil was considered to be a vehicle for phenol in peel formulas. In 1999, Gregory P. Hetter wrote a four part series challenging the assumptions surrounding phenol-based chemical peeling. He found that increasing concentrations of phenol without croton oil caused skin reaction but no significant peeling effect. Moreover, he found that the depth of the peel was dependent on concentration of croton oil rather than phenol[20,21,22].

Phenol (C_6H_5OH) is an aromatic hydrocarbon. In its pure form it is a fluid (phenol USP), 88% phenol and 12% water. The Baker-Gordon-formula contains 50-55% phenol.

Baker-Gordon-formula

Phenol 88%	3g
Aqua dest	2g
Hexachlorophen 0.23% in propylenglykol	8g
Croton oil	3g

Deep peels with Baker-Gordon-solution are severe skin aging, acne scars and actinic keratosis[23]. Baker-Gordon-solution is particularly applicable for the treatment of precancerous lesions on the forhead and capillitium. However, most studies concentrate on the treatment of rhytides. A significant improvement, particular in the perioral region has been repeatedly described[24].

The Baker-Gordon-solution reveals an edema and massive inflammation of the epidermis and dermis, followed by epidermal necrosis, regeneration, cell migration out of the sebaceous glands. Histologic studies revealed an increase of elastic and collagen

fibers even 20 years after the peel[25]. This deep peel has been established more than 40 years ago and is now during times of "Laser skin resurfacing" the golden standard. However, seriell studies have lately demonstrated that not phenol but croton oil dissolved in phenol is the actual peeling agent[20,21,22].

Croton oil (*Crotonis Oleum*) is an oil prepared from the seeds of *Croton Tiglium* a tree belonging to the natural order *Euphorbiaceae* and native or cultivated in India and the Malay Archipelago. Due to the caustic exfoliating effects it has on the dermal components of the skin in conjunction with phenol solutions, it results in an intense reaction which leads to initial skin sloughing and then eventual regeneration of more youthful skin architecture.

For man 8-15 g of phenol is toxic. Higher concentration and application of larger skin areas may damage myocardial, kidney and liver function. If applied on the skin surface 70% of the applied phenol is absorbed within 30 minutes, 75% thereof is excreted and 25% metabolized to CO_2 and H_2O.

If applied careful, the total amount of phenol used for a total face peel is less than 1g. Toxicity is not expected at that concentration. If a full-face peel with phenol is performed too rapidly, i.e. within less than 30 minutes, a 20% chance of arrythmia has been calculated[26]. Therefore, a full face peel (less than 9% of the total body surface) must be extended to at least 60 minutes.

Phenol is bactericidal, therefore infections are rare. Side effects, such as milia, hyperpigmentation and telangiectasia are more transitory. During the immediated post peel healing time, pruritus can be minimized with ice, steroids and aspirin. The ideal patient for a deep Baker-Gordon Peel is a skin-type I – II patient.

Conclusion

Evaluating the current literature on the efficacy of chemical peeling procedures with GA, SA or TCA, it is evident that most recent studies focus on GA as cosmetic ingredient. Epidermal and dermal effects of AHAs could be demonstrated as follows:

1. decrease in the number of SC layers
2. barrier structures of the SC are not disrupted by GA formulations at the concentrations used
3. the epidermis increases in thickness with increased mucopolysaccharides
4. increased density of dermal collagen
5. improved quality of elastic fibers
6. reduction of UV-induced skin tumor development in mice.

There are few recent studies on thse use of GA as a peeling agent: Epidermal and dermal regeneration do not seem to correlate with the degree of irritation and inflammation. The well-documented clinical effects need scientific proof, which at present is only vaguely extractable from the literature. SA as a peeling agent has been studied in mice: Epidermal and dermal structures reorganize after GA and SA peels, followed by a reduction of UVB-induced skin tumors. This effect has not been observed in TCA peels.

Long-term effects on proliferation are not well documented. Fibroblasts cease to respond after 50-60 cycles. Repeated peels frequently damage the dermis, and the immune system may be compromised. Chronic acceleration of skin regeneration in advanced age may lead to a shorter rather than extended youthful skin appearance.

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