

Melasma: A comparative study of the combination of glycolic acid and hydroquinone in association with glycolic acid peelings

Melasma: Estudio comparativo de una asociación de ácido glicólico con hidroquinona y peelings de ácido glicólico

Fernando S. Macedo, Silvia Karina Kaminsky, Edileia Bagatin, Karine M. Hassun, Sergio Talarico

Department of Dermatology. Universidade Federal de Sao Paulo. Sao Paulo. Brazil.

Correspondence:

Fernando S. Macedo
Universidade Federal de Sao Paulo
R. Estado de Israel, 192, Vila Clementino
CEP 04022-000 Sao Paulo. SP Brazil
Phone: (+55) 11 5549 7888
Fax: (+55) 11 5572 7670
E-mail: fmacedo22@yahoo.com.br

Abstract

Melasma is a common acquired pigmentation disturbance, found mainly in women and located generally in those areas of the face most subject to sun exposure. Photoprotection and depigmenting agents, such as hydroquinone, are used in order to lighten the marks. There is, however, some controversy regarding the use of chemical peelings in the treatment of melasma.

To compare the efficacy of a depigmenting cream plus sunprotector alone to this same approach in combination with 70% glycolic acid peelings in the treatment of melasma.

Eight female patients participated in a split-face prospective study that lasted seven months. During the first month they were oriented to only use a cream containing 10% glycolic acid and 4% hydroquinone as well as sun protector, on both sides of the face. A sequence of 4 peelings using 70% glycolic acid were then applied to one side of the face while only the peeling vehicle was applied to the other side. After 30 days, the application of the peelings and placebo was repeated on inverse sides of the face. The treatment was evaluated using clinical pictures assessed by 3 independent dermatologists.

Most of the patients showed improvement in their melasma with the use of the 10% glycolic acid and 4% hydroquinone cream together with adequate sun protection. The application of 70% glycolic acid peelings did not result in lightening of the melasma, and the inversion of the sides receiving peelings or placebo confirmed this result.

The use of 10% glycolic acid and 4% hydroquinone cream together with adequate sun protection is effective in the treatment of melasma. The application of 70% glycolic acid peelings did not produce additional improvement in the lightening of the affected skin.

(Macedo FS, Kaminsky SK, Bagatin E, Hassun KM, Talarico S. Melasma: A comparative study of the combination of glycolic acid and hydroquinone in association with glycolic acid peelings. Med Cutan Iber Lat Am 2006;34:11-16)

Key words: Melasma, glycolic acid, hydroquinone, peeling.

Resumen

El melasma es una alteración adquirida de la pigmentación, frecuente, predominante en las mujeres y habitualmente localizado en las áreas de mayor exposición solar de la cara. En el tratamiento de las manchas normalmente se emplean despigmentantes, como la hidroquinona, y fotoprotección. Existen controversias sobre el beneficio de los peelings químicos en el tratamiento del melasma.

Comparar la eficacia de una crema despigmentante y un fotoprotector usados aisladamente, así como asociados a peelings de ácido glicólico al 70% en el tratamiento del melasma.

Ocho pacientes del sexo femenino participaron en un estudio prospectivo que duró siete meses. Durante el primer mes las pacientes usaron solamente crema con ácido glicólico 10% e hidroquinona 4%, además de fotoprotector, en ambos lados de la cara. Se aplicó, entonces, una secuencia de 4 peelings de ácido glicólico al 70% en un lado de la cara y en el otro lado solamente el vehículo del peeling. Después de 30 días, se realizó una nueva aplicación del peeling y del placebo en lados inversos de la cara. Tres dermatólogos realizaron la evaluación independiente de las fotos clínicas.

La mayoría de los pacientes tuvo mejora del melasma con el uso de la crema con ácido glicólico al 10% e hidroquinona al 4% asociado a la fotoprotección adecuada. La aplicación de los peelings de ácido glicólico al 70% no produjo aclaramiento del melasma en comparación al placebo y la inversión de los lados de la aplicación confirmó este resultado.

El uso de la crema con ácido glicólico al 10% e hidroquinona al 4% asociado a la fotoprotección adecuada es efectivo en el tratamiento inicial del melasma. La aplicación de peelings seriados de ácido glicólico al 70% no produjo mejora adicional en el aclaramiento de la piel.

Palabras clave: Melasma, ácido glicólico, hidroquinona, peeling.

Melasma is a common acquired disturbance of the pigmentation that is characterized by irregular symmetrical hyperchromic macules, with color tones that vary from light brown to black. There is a direct correlation between their location and those areas of the face subject to greatest sun exposure: forehead, dorsal nasal, upper lip, infra and supraorbital margins, zygomatic process and angle of the jaw[1]. Their location is also influenced by the increased number of melanocytes present in the epidermis of the face and forearms, approximately double, in comparison to the rest of the body[2].

Women represent 90% of cases[3,4], and there is predominance among individuals with darker skin (phototypes IV to VI) and Hispanic or Asian descendents[5]. A family history of melasma is found in about 30% of the cases[6, 7]. The marks appear at the end of the third or beginning of the fourth decade of life[8, 9], though in black patients they may appear later[3].

A number of factors may contribute to the etiopathogenesis of melasma. Stimulus from ultra-violet radiation on melanocyte activity is the main one. The skin in the area of melasma has a higher degree of photoaging and an increased number of melanocytes when compared to the adjacent unaffected skin[1, 2].

Melanogenesis stimulated by estrogen in pregnancy or due to the use of hormonal anti-contraceptives may also provoke or aggravate melasma[6,10]. Other causes such as dysfunctions of the ovary[11], thyroid[12], adrenal glands, the use of cosmetics[8], and medicines (quinacrine, phenylhydantoin) may be involved.

Melasma is a common dermatosis[13] and may appear in a very intense form with significant psychosocial repercussion[5].

Treatment is mainly focused is sun protection, because of the stimulus given to melanocyte activity by ultra-violet radiation[14]. This may be observed in clinical practice with the worsening of the melasma in summer and its improvement in winter as well as by the great possibility of relapse after sun exposure. The use of sun protection alone is sufficient to promote improvement of melasma[4, 14].



Figure 1. Clinical aspect before treatment: observe the dark brown melasma in the chin, upper lip, malar region, dorsal nasal, and front.

Hydroquinone is the most used depigmenting agent that blocks melanogenesis. It is a tyrosinase inhibitor, and therefore, inhibits the transformation of tyrosine into dopa and dopaquinone and, consequently into melanin. Hydroquinone used in high concentrations increases the possibility of irritative reactions, the risk of ochronosis[15], and does not increase effectiveness. Other chemical agents like tretinoin, corticosteroids and alpha-hydroxy-acids can be used in association with hydroquinone in the treatment of melasma[9, 16, 17]. Glycolic acid diminishes the barrier function of the corneum stratum and accelerates the epidermic turnover, and when used in association with hydroquinone increases its depigmenting action[18].



Figure 2. Clinical result after 1 month using only the depigmenting cream (10% glycolic acid and 4% hydroquinone) and adequate sun protection: observe lightening of melasma in all areas.



Figure 3. Clinical result at four months after beginning; 1 month after a sequence of four glycolic acid peelings on the left side and placebo on the right side: observe the lightening of the entire face and a slight better result on the placebo side, since we can observe darker spots on the left upper lip and around left eye.

Chemical peelings can be used in the treatment of aging and skin pigment alterations. In the treatment of melasma, superficial peelings are the most recommended, as the more aggressive treatments like medium and deep chemical peelings and the use of lasers or intense pulsed light have not been shown to be effective. These procedures also offer greater risk of post-inflammatory pigmentation, hypochromia, and the formation of scars and cheloids[16, 19, 20].

Recently, dermabrasion has shown good results in the treatment of melasma[21]. However, patient's down-time is long, it also presents increased risk of adverse effects and requires further study in order to prove its efficacy.

There are conflicting reports in the literature on the benefits of superficial and medium peelings in the treatment of melasma[9, 10, 17, 22, 23, 24]. Glycolic acid is an alpha-hydroxy acid that, in low concentrations, reduces epidermic cohesion and may facilitate the penetration of the depigmenting agent. Used as a peeling agent in concentrations of 50 to 70% it may cause epidermolysis[24]. Its use may augment the effect of topical treatments and assist the removal of melanocytes and epidermic melanin.

We proposed the nocturnal use of a formulation with 2% hydroquinone combined with 10% glycolic acid because of

its depigmenting effect and low risk of side effects, together with the use of a photoprotector cream (SPF=15) during the day. In association with this procedure, patients received a sequence of 70% glycolic acid peelings to evaluate its efficiency in the treatment of melasma in comparison to the use of topical treatment alone.

In order to eliminate the variability between the patients and the possible difference in skin care we proposed a comparative split-face study. As well as the nocturnal topical treatment and the diurnal photoprotection on the whole face, the patients underwent a sequence of 70% glycolic acid peelings on one side of the face, while on the other side, only the peeling vehicle was applied.

Materials and methods

Patients. Nine females were submitted to treatment, though one was excluded from the evaluation because of the poor quality of the initial photograph. The patients were Fitzpatrick phototypes II to V and aged from 23 to 65 years. The exclusion criteria included pregnancy, use of hormonal contraceptives, previous use (within 30 days) of any depigmenting agent or topical and systemic corticosteroid,

concomitant treatment of any illness, and any history of hypersensitivity to any of the components of the formulations. The patients were informed of the possible risks and benefits of the treatment and were able to withdraw from the study without loss of any form. All the patients were instructed to use the night-time formula with 10% glycolic acid and 4% hydroquinone in buffered anionic cream (pH = 4) on a daily basis and apply photoprotector cream (SPF = 15) 3 times a day until the end of the study. After 30 days using the night-time cream, a sequence of four glycolic acid peelings (70%), non-buffered (pH=1) in natrosol fluid gel were applied on the left side of the face, and only the vehicle on the right. The interval between peelings was 15 days. After 30 days, the patients underwent four more sessions of peelings. This time the application was done on inverted sides of the face, that is; 70% glycolic acid on the right and natrosol on the left side with the aim of promoting a homogenous result on both sides. The post-peeling guidance emphasized the use of sunprotector and the re-initiation of outpatient treatment 3 days after the procedure.

All the materials used in the study (depigmenting cream, sunprotector, defatting solution, glycolic acid peeling in gel and its vehicle) were supplied by Drogaderma pharmacy of laboratory operations (São Paulo, SP).

Peeling application. Initially the skin of the patients was defatted with gauze soaked in a solution with equal parts of alcohol ether and acetone. Following this, gloved fingers were used to apply the 70% glycolic acid in natrosol gel on one side of the face and only the vehicle (natrosol gel) on the other. With the appearance of light erythema, without the presence of frosting or with very discreet frosting, (after approximately 1 to 3 minutes) the peeling was removed with physiological serum and, shortly after, the sun protector was applied.

Evaluation. Independent clinical evaluation was done by three dermatologists from standardized full-face photographs in the front position and the right and left profiles. The first evaluation was made comparing the photos taken before beginning the topical treatment with those taken after thirty days of using the depigmentation cream (pre-peeling photo) to observe the improvement attained in the period. The effect of the glycolic acid peelings was evaluated by comparing the photos obtained 30 days after the first sequence of peelings (3 months after the start of the peelings) and those taken 30 days after the application on inverted sides of the face (6 months after the start of the peelings), with the pre-peeling photos.

The object of this analysis was to compare the intensity and extension of the marks at each stage, using the following scale:

- Worsening of the clinical condition (-1)

- Unaltered (0)
- Slight improvement (1); lightening of 0 to 33% of the marks
- Moderate improvement (2); lightening of 34 to 66% of the marks
- Accentuated improvement (3); lightening of over 66% of the marks

Results

The use of the depigmenting cream (10% glycolic acid and 2% hydroquinone) was well tolerated; a few episodes of erythema and slight burning were alleviated by reducing the frequency of application of the cream (use on alternate nights for 7 to 10 days) and by the introduction of a mild emollient cream. The application of the 70% glycolic acid peeling immediately produced erythema and burning sensation and a fine peeling of the skin that lasted 3 to 5 days. There was no formation of vesicula, scar or dischromia after the application of the peeling.

Of the eight patients that took part in the study, five (62.5%) presented improvement to the melasma after using the nighttime depigmenting cream and daytime photoprotector for thirty days; four presented a slight improvement and one patient had an accentuated improvement. The evaluation performed thirty days after the sequence of four glycolic acid peelings (left side of the face) revealed that: six patients (75%) did not show any alteration to the clinical condition, there was one patient with a slight improvement and one patient with a slight worsening of clinical condition. Within this same period, on the right side of the face, which received the placebo (natrosol gel), five patients (62.5%) presented no alteration, two improved (1 showed a slight improvement

Table 1. Results.

Patient	Age	Phototype	1 month	4 months placebo/glycolic	7 months glycolic/placebo
CCB	40	V	+1	+1/0	0/0
DVD	26	II	+3	0/0	0/0
MIGS	59	II	+1	0/0	(***)
SO	43	IV	+1	+2/+1	0/0
LTM	65	III	0	0/0	0/0
CAL	25	II	+1	0/0	0/0
MCS	31	IV	0	0/0	0/0
RXS	23	V	0	-1/-1	+1/0

(***) This patient was not submitted to the inverted application of the peelings, but merely maintained the night time cream and photoprotector treatment.

and the other moderate) and one patient showed worsening. The latter patient (phototype V) presented worsening in both sides of the face and reported significant sun exposure without adequate sun protection during the period.

The analysis obtained thirty days after the inversion of the side of the face in the application of the glycolic acid peeling showed similar results. In one patient the inversion was not carried out as she was satisfied with the result. On the right side of the face (to which the glycolic acid peeling was applied), five patients (71.4%) had no alteration and two (28.5%) showed a slight improvement. On the left side, (to which the natrosol gel was applied), 6 patients (85.7%) had no alteration and 1 patient presented a slight improvement (14.3%)(Table 1).

Comment

The treatment of melasma remains a challenge and its results frequently produce the dissatisfaction of the physician and the patient. The anatomopathological and ultra-structural analysis of the skin with melasma, in comparison with the adjacent non-lesioned skin, shows a greater degree of photoaging, larger melanocytes with hyper activity (more dendrocytes), and increase in its number[1, 2]. These differences may explain the increase in melanin in all the layers of the epidermis in relation to the adjacent non-lesioned skin, as in the latter, the accumulation only occurs in the basal layer. Only a minority of patients with melasma (12%) present an increase in dermal melanin[1]. Currently, there is no possibility of definitively modifying the functioning of the altered melanocytes present in the epidermis and impede the recividity of the melasma[10].

Of the topical treatments, hydroquinone is the most widely used and the most effective. Used at a concentration of 2% it is as effective as at higher concentrations (4 to 6%) and presents lower rates of side effects[25, 26] like irritative contact dermatitis and allergy, post inflammatory pigmentation and discoloration of the nails and eyebrows. Several researchers have reported better results when hydroquinone is used in association with other chemical agents. In association with tretinoin (used in a concentration of 0.025 to 0.1%) and with topical corticosteroids (dexamethasone at 0.1%, hydrocortisone acetate at 1% or betamethasone valerate at 0.1%), hydroquinone has been shown to be more effective though with a greater possibility of side effects[29, 30].

Low concentrations of glycolic acid (10%) reduce the adhesion between the corneocytes, the corneum stratum[27] and lead to a reduction in its barrier function. Used in association with hydroquinone it augments the depigmentation effects of the latter[18] and used in a concentration of 10% presents a low risk of side effects. In this study, the use of this combination presented mild and transitory side effects,

like erythema and burning sensation that regressed with less frequent use (alternate nights) and the use of mild emollients for some days. The use of the formula for thirty days prior to applying peelings produced a slight improvement in 4/8 (50%) patients and moderate improvement in 1/8 (12.5%) of the patients. This is probably due to the reduction in the production of melanin and of its transference from the melanosomes to the epidermis.

Glycolic acid used at a 70% penetrates the stratum corneum, provokes rapid epidermolysis (in few minutes), made apparent by the frosting, and can lead to the mechanical removal of the epidermis[18, 28]. The application of a series of 4 peelings with 70% glycolic acid was well tolerated by the patients and did not present adverse effects like dischromia or scars. The sequence of peelings on one side of the face was shown to be ineffective in improving melasma when compared with the application of the vehicle on the contralateral. The inversion of the sides to which the peelings were applied confirmed this finding.

The use of superficial chemical peelings can help in the treatment of melasma, though its results remain controversial. Some authors have demonstrated improvement in melasma with superficial peelings like 70% glycolic acid, Jessner solution[17] and 30% salicylic acid[23], though there has been no separate analysis of the benefits of the use of depigmenter (hydroquinone) used in association with the treatment.

Sarkar et al[24] demonstrated a more rapid and intense improvement in melasma after a sequence of peelings using glycolic acid at 30% (3 application) and 40% (3 applications) when compared to the use of only a topical treatment which consisted of a combination of tretinoin 0.05%, hydroquinone 4% and hydrocortisone acetate 1% in cream. In spite of being a well conducted study and having a large number of patients, it does not present a split-face methodology which would be the most appropriate to eliminate any individual variability bias in the response to the treatment and in the care taken with photoprotection.

Hurley et al.[22] did not show improvement in melasma with the application of a sequence of peelings with glycolic acid at 20% and 30%. Despite presenting an ideal methodology and objective evaluations of the treatment, the low concentrations of glycolic acid used in the treatment could influence the results. Lim et al.[9] demonstrated improvement, though not statistically significant, in melasma after a sequence of 8 peelings of glycolic acid at concentrations of 20 to 70% when compared to the use of a cream containing 10% glycolic acid and 2% hydroquinone on the other side of the face. The improvement however, was only observed after the initiation of the 70% glycolic acid peelings. The epidermolytic effect of 70% glycolic acid could justify the result.

This situation represented the motive behind the present pilot study, using peelings with glycolic acid at a concentration at 70% that had been shown to be the most effective in the above study. Despite not revealing clinical improvement in the melasma in comparison with the use of daily depigmenting treatment, glycolic acid peelings produced an improvement, though not measured, in skin quality with regard to texture, radiance, and among other pre-existing pigment alterations observed by the physicians and patients. This effect probably contributed to the superior results in the subjective evaluations of the patients when compared to objective evaluation made with regard the melasma[22] and

enhances the degree of patient satisfaction even when there is no effective improvement in the melasma.

Conclusion

Based on this simple study we can conclude that the daily use of a cream containing 10% glycolic acid and 2% hydroquinone together with adequate photoprotection can improve melasma, mainly at the initial stages of treatment. The use of a series of 70% glycolic acid peelings did not produce any additional improvement beyond that seen with the initial depigmentation.

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