Review Article

Treatment of melasma: systematic review

ABSTRACT

Introduction: melasma is an acquired hypermelanosis of sun-exposed areas. The pathophysiology of melasma is uncertain. The most important factor in the development of melasma is exposure to sunlight, but also it has been described in relation to hormonal factors, vascular, genetic predisposition, proteins related to tyrosinase. Due to its refractory and recurrent nature, the treatment of melasma is often difficult. The goals of treatment often include prevention or reduction of the affected area with the fewest possible adverse effects. The principles of therapy include protection against UV radiation, the inhibition of activity of the melanocytes and melanin synthesis. **Objectives:** to conduct a systematic review to identify the most effective and safe treatment, including topical treatments, oral treatments and surgical procedures, for the melasma. **Method:** the study was conducted in the period from February, 05 to March, 15 2009, using 3 databases: MEDLINE (1966-2009), Cochrane Library and LILACS. After establishing criteria for the selection of studies, the best controlled and comparative studies were described individually. **Results:** We found 703 articles in MEDLINE, 89 and 100 in LILACS and Cochrane Library, reviewed 143 articles of which 10 were descriptive studies (6,99%), 30 review (20,97%), 103 randomized controlled trials (72,03%). Descriptive studies and reviews were analyzed together. Forty two articles with the best design were chosen for individual description. 12/42 included controlled studies (28,57%) or 30/42 comparative (71,43%), like split face (18) or parallel groups (24), and 34 (80,95%) randomized. 8 (19,05%) had the ideal design, i.e. blind placebo-controlled. **Limitations:** heterogeneity of the studies, few with good methodological quality. **Conclusions:** The use of broad-spectrum sunscreen is important, as is topical hydroquinone, the most common treatment for melasma. Other lightening agents include retinoic acid, azelaic acid, kojic acid and others. Combination therapies increases efficacy as compared with monotherapy. Chemical and physical peels, laser treatments, and intense pulsed light therapy are additional modalities that have been used to treat melasma.

INTRODUCTION

Melasma is an acquired hipermelanosis that affects sun-exposed areas, especially the frontal and malar[1,2,3,4,5] regions. It affects both sexes with higher incidence in women, especially pregnant ones[2,3,5]. It occurs in all races, particularly in individuals with high phototypes, who live in areas with high levels of ultraviolet radiation (UV)[4,6,7]. The pathogenesis of melasma is not yet well understood. The UV radiation is an important factor involved in peroxidation of lipids in the cell membrane, with release of free radicals which stimulate the melanocytes.[3,5,6]

It has been described a direct relationship between female hormonal factors and melasma, with studies showing high levels of luteinizing hormone (LH) and low serum estradiol.[3,5,6] It is also suggested a vascular etiology where the melanocytes, which have growth factor receptors of vascular endothelial (VEGF), could respond to angiogenic factors, increasing the blood and contributing to skin hyperpigmentation.[8] Furthermore, electronic microscopy demonstrates synthesis of tyrosinase increase in the lesions of melasma.[7] The familial occurrence suggests genetic predisposition. The melasma is classified according to clinical and histological[7] features. Regarding the location of the pigment, it may be epidermal, dermal or mixed.[3,4,5] This classification is particularly important to define the prognosis and therapeutic choice.[1,3]

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The treatment of melasma has as main objective the clearing of lesions and the prevention and reduction of the affected area with the fewest possible adverse effects.[4,9] The main agents used and their mechanism of action are described in Chart 1.Additional recommendations include discontinuation of contraceptive pills, fragrance cosmetics and phototoxic drugs.[10] Other ways of treatment can be used in chemical peelings, microdermabrasion, intense pulsed light and lasers.[11]

OBJECTIVES

To perform a systematic review of the literature to identify more effective and safe treatments for melasma, including topical, oral and by means of interventions.

Table 1 - Mechanism of action of main bleaching agents used to treat melasma (adapted Gupta et al., 2006)

Machanism of action	Substance
Tyrosinase inibition	Hydroquinone Tretinoin* Azelaic Acid Kojic Acid
Non-selective suppression of melanogenesis	Corticosteroids
Inhibition of reactive oxygen species	Azelaic acid
Melanin removala	Chemicals peeling
Termal damage	*Laser*

* tretinoin may also remove the pigment granules of the keratinocytes and accelerate epidermal turnover[12]

METHODS

Search strategy and selection of studies

The searches were conducted in the period from February 05 to March 15 2009, using 3 databases: MEDLINE (1966-2009), Cochrane Library (March 2009) and LILACS, in English, Portuguese and Spanish. The keywords used were: melasma, Chloasma and terms like: treatment, *tratamiento*, therapeutics, efficacy, safety, review, update, randomizade clinical trial. 703 articles in MEDLINE, 89 in LILACS and 100 in the Cochrane Library were found and 143 studies were selected for review, using the methodological quality as an exclusion criterion. Considering the proposed objective, 42 individual studies were analyzed. They have compared at least one active with a control treatment, which may be a placebo or an alternative. The other studies were analyzed together for descriptive purposes.

The studies were categorized according to the type of therapeutic agent used: topical bleaching, chemical peelings, microdermabrasion, intense pulsed light, lasers, among others. It was included in these categories the controlled or comparative studies, randomized or not, blind or open.

METHODOLOGICAL QUALITY

The methodological quality of studies was assessed according to the following criteria: adequate randomization; group control with placebo in the same patient or in parallel groups; blinding to patients and / or researchers; criteria for inclusion and exclusion of people at the study clearly described; technique adequately described; evaluated effectiveness including quantitative methods - melasma Severity Index or MASI, quantitative digital analysis of photographs, invasive methods such as biopsy of the skin and histological examination with special staining, immunohistochemical and digital analysis - tolerance and immediate safety properly assessed, statistical analysis included, and monitoring of patients to assess the maintenance of the results by pre-set.

RESULTS

Of the 143 articles selected for review, 10 were descriptive (6.99%), 30 Review (20.97%) and 103 intervention (72.03%). The uncontrolled intervention, descriptive and revision studies were analyzed together. Of the remaining articles, 42 were selected to best design for individual description. 12/42 included controlled studies (28.57%) and 30/42 comparisons (71.43%), split face type (18) or parallel groups (24), and 34 (80.95%) were randomized.[8] Some articles (19.05%) had the ideal design, i.e. blind placebo-controlled. The main studies are described according to the type of treatment and substances used.

Sunscreens

Vazquez 1983[13]: a controlled, randomized and double-blind study evaluating the use of sunscreens with high spectrum versus placebo in 53 patients using bleaching creams. These results confirmed the positive impact of the use of sunscreens in the treatment of melasma (96.2% versus 80.7%).

Abarca 1987[14]: a controlled, randomized and double-blind study, in 65 pregnant women using sunscreen versus placebo daily in face during the second trimester of pregnancy. There was a significantly lower incidence of melasma in the group who used sunscreen.

Hydroquinone

Sanchez 1982[15]: a comparative, randomized and double-blind study, between 2 formulations of hydroquinone (HQ) in 50 women (Formula A - HQ 3% + 0.2% ascorbic acid in

hydroalcoholic solvent; formula B - identical the formula A + emollient agents Laneth - 16 3.0% and PPG - 15 Stearyl Ether 2.0%) twice a day. The A formula has been most effective with significant improvement in 88% of patients, with minimal adverse effects.

Retinoids

Leenutaphong 1999[16]: a controlled and randomized study between topical use of isotretinoin gel 0.05% versus base vehicle on 30 patients with moderate to severe melasma for 40 weeks. The average reduction of MASI and Mami (colorimetric evaluation index) in the isotretinoin group was 68.2% and 47% respectively, versus 60% and 34% in the group control, without statistical difference.

Kimbrough-Green 1994[17]: a controlled, randomized and blinded study comparing the use of topical tretinoin 0.1% versus vehicle in 28 black patients by 10 months. There was clinical improvement and color, with enhancement in MASI 32% in the tretinoin group versus 10% in the control group. Histological examination revealed significant reduction in epidermal pigment in the tretinoin group.

Griffiths 1993[18]: a controlled and randomized study between topical tretinoin 0.1% versus vehicle in 38 women for 40 weeks. In the tretinoin group there was 68% of clinical improvement versus 5% in the control group ($p = 0.0006$). Colorimetry has showed clearance of tretinoin group and browning in the control group ($p = 0.01$), which was correlated to clinical clearance ($r = 0.55$, $p = 0.0005$). Histologically, the epidermal pigment was reduced by 36% in the tretinoin group and increased by 50% in the control group ($p = 0.002$), which was also correlated with clinical clearance ($r = -0.41$, $p = 0.01$).

TOPICAL COMBINED TREATMENTS

Grimes 2007[19]: a comparative and split-face study, using 3 creams with HQ 4%: cream A (4% HQ + retinol 0.15% with antioxidants), cream B (4% HQ + retinol 0, 3% with antioxidants), cream C (fluocinolona acetonide 0.01% + HQ 4% + tretinoin 0.05%) for 12 weeks. Patients were divided into 2 groups: group 1 - cream A versus B, group 2 - cream A versus C. In group 1, cream A has obtained statistically significant improvement compared to cream B, the total assessment of the severity of the disorder (week 8, $p = 0.05$, week 12, $p = 0.028$), area of injury (week 8, $p = 0.005$, week 12, $p = 0.012$), intensity of pigmentation (week 8, $p = 0.012$, week 12, $p = 0.012$) and MASI score (week 8, $p = 0.002$, week 12, $p = 0.012$). Group 2 has showed similar results between the cream A and C.

Ferreira 2007[20]: a comparative, randomized and open study between the use of HQ 4% versus retinoic acid 0.05% + 4% HQ + fluocinolona acetonide 0.01% in 120 patients for 8 weeks. There was total clearance in 35% of patients receiving triple therapy versus 5.1% of those who received only HQ ($p = 0.0001$). There was a greater improvement of 75% in 73% of patients using triple therapy versus 49% who received HQ 4% ($p = 0.007$).

Chan 2008[21]: a comparative, randomized and blinded study from the use of tretinoin acetonide 0.05% + 0.01% of fluocinolona HQ + HQ 4% versus HQ 4% for 8 weeks. The combined therapy was superior to monotherapy, showing better performance as MASI in 64.2% versus 39.4% of the HQ group ($p<0.001$). The patient's satisfaction was also higher in the combined therapy group with 70.8% versus 49.6% in the HQ group ($p = 0.005$).

Astaneh 2005[22]: a comparative, randomized and double-blind study in 64 patients divided into 2 groups (Group A: HQ 4% versus Group B: 4% HQ + dexamethasone 0.05% + tretinoin 0.05%). After 12 weeks, 81.2% in group B compared with 31.3% in group A had good to excellent results ($p<0.05$).

Cestari 2007[23]: a multicentre, comparative, randomized and open study with 120 patients using triple combination (TC) of HQ 4% + tretinoin 0.05% + fluocinolona acetonide 0.01% once a day versus HQ 4% twice a day to assess the cost benefit of treatment. After 8 weeks, treatment success was achieved in 35% of patients in the TC group and 5.1% in the group with HQ. CT shows higher efficiency and lower cost per case of complete clearance of melasma, as compared with HQ 4%.

Taylor 2003[24]: a multicentre, comparative, randomized and single-blind study in 641 patients divided into treatment groups, using tretinoin 0.05% cream containing HQ 4% + fluocinolona acetonide 0.01%, versus the combination of double agents (tretinoin + HQ, tretinoin + fluocinolona acetonide and HQ + fluocinolona acetonide) for 8 weeks. The result has showed that 26.1% of the group experienced complete clearing triple therapy versus 4.6% of the other groups ($p = 0.0001$). Furthermore, a reduction in pigmentation of 75% in more than 70% of patients was observed in the triple therapy group versus 30% of the double combination.

Guevara 2003[25]: a comparative, randomized and double-blind study in 39 Hispanic women divided into 2 groups. Group 1: HQ 4% cream with glycolic acid 10% + vitamin C + vitamin E. Group 2: sunscreen. After 12 weeks, there was improvement in 75% of the group that received the bleaching cream versus 13% of the sunscreen group ($p<0.0001$).

Lim 1999[26]: a comparative, randomized, double-blind and split-face study between HQ 2% cream + glycolic acid 10% versus HQ 2% + KOJIC acid 2% in 40 Chinese women with epidermal melasma for 12 weeks. There was an improvement

of 60% in the group that received KOJIC acid and 47.5% in the group that has not received it, no statistically significant difference (p = 0.9).

Garcia 1996[27]: a comparative, split-face study between the use of gel with glycolic acid 5% + HQ 2% versus glycolic acid 10% + KOJIC acid 2% in 39 patients for 12 weeks. All patients had some degree of improvement. Patients with epidermal type melasma have responded better to treatment with 28% in KOJIC acid group and 21% in the hydroquinone group, but without statistically significant difference (p>0.05).

Sarkar 2002[28]: a comparative, split-face, randomized and single-blind study, in 40 Indian patients, using on one side of the face a cream with clobetasol propionate 0.05% followed by 8 weeks of azelaic acid (AZ) 20 % during 16 weeks versus AZ 20% per 24 weeks. By the 16th week the clearance was more evident in the sequential therapy with 70% versus 33% (p<0.001). However, at 24 weeks the two sides had good response with clearance of 86% versus 50% (p = 0.0052) although the difference also statistically significant.

Lee 2002[29]: a controlled and randomized study in 47 Korean women divided into three groups. Group A received vehicle only. Group B received lincomycin 2% + betamethasone valerate 0.05%, and group C received lincomycin 2% + linoleic acid 2% + betamethasone valerate 0.05%. After 6 weeks, group A remained 98% with the initial MASI and Group B with 85.4%, both without statistical significance. Group C was reduced to 68% of the initial MASI (p<0.05).

HQ X Azelaic acid (AZ)

Balin 1991[30]: a comparative, randomized and double-blind study between AZ 20% versus HQ 4% in 329 women. After 24 weeks, 64.8% of the AZ group and 72.5% of the HQ group has showed good to excellent results, but 7.4% and 8.3% respectively, had treatment failure. There was no difference between groups in the reduction of the size of the lesion and the intensity of pigmentation.

HQ X Ascorbic acid

Espinal-Perez 2004[31]: a comparative, split-face, randomized and double-blind study using a cream with acid Ascorbic 5% versus 4% HQ in 16 women. After 16 weeks, the subjective evaluation showed good to excellent results in 93% on the side of the HQ compared with 62.5% on the side with ascorbic acid (p<0.05), however, colorimetric measures has showed no statistically significant differences.

HQ X Skin whitening complex

Haddad 2003[32]: a controlled, split-face, randomized and double-blind study in 30 women divided into 2 groups. Group 1: HQ 4% in one side of the face and placebo on the other side. Group 2: Skin Whitening complex 5% and placebo. After 3 months, there was a global improvement of 72% in treated hemiface compared to placebo. Group 1 has showed an improvement of 76.9% with 25% of mild adverse effects and group 2 has showed improvement of 66.7% without adverse effects. However, there was no statistically significant difference between groups (p = 0.673).

Amelan X mela D

Levy 2005[33]: a comparative, randomized and split-face study in 22 French women using bleaching creams without HQ: Amelan M® once a day on a hemiface versus Mela D® once a day on the other hemiface. The evaluation after 4 months has showed statistically significant reduction in MASI with the two treatments, and in a measured analysis of melanin (mexameter MX18®), only AMELAN M has showed depigmentation (p<0.00001).

Rucinol

Khemais 2007[34]: a controlled, split-face, randomized and double-blind study in 32 women, using rucinol serum 0.3% versus vehicle to be applied at each hemiface twice a day. After 12 weeks, it was given an option for patients to participate in an extra time (3 months) with rucinol across the face (Stage 2). At the end of phase 1, it was observed that the MASI for the side treated with rucinol was significantly lower than the control side (p = 0.027). In phase 2, the side previously treated with vehicle showed significant reduction of the score as well as on the already treated with rucinol, but no statistically significant difference between the 2 sides.

Niacinamide Hakozaki 2002[35]: a controlled, split-face, randomized and double-blind study in 18 Japanese women. Niacinamide topical use 5% versus vehicle for 8 weeks. Subjective evaluation and imaging have showed significant reduction of pigmentation in the treated side in the control (p<0.05).

Hakozaki 2006[36]: a comparative study, split-face and randomized study in 60 Japanese women divided into 2 groups, each group with 2 treatments (one in hemiface). Group 1: Gel with Vitamin C and Niacinamide + ultrasound (US), no treatment in another hemiface. Group 2: Gel with Vitamin C and Niacinamide + US versus the same gel. After 4 weeks, there was a significant reduction of hyperpigmentation on the sides treated with gel-vitamin C + Niacinamide associated with the US compared to the untreated side or by using just the bleaching gel.

Liquiritin

Amer 2000[37]: a controlled, split-face, randomized and blinded study in 20 women comparing the topical use of liquiritin versus vehicle twice a day for 4 weeks. The assessment

of 5 points score compared to normal skin (1, no difference; 2, slight difference; 3, moderate difference; 4, substantial difference; 5, very marked differences) has showed reduction in levels 1 to 3 on the side treated with liquiritin.

Intophoresis With Vitamin C

Huh 2003[38]: a controlled, split-face, randomized and double-blind study in 29 women using iontophoresis for the solution of vitamin C on one side of the face versus distilled water on the other side. Colorimetric evaluation after 20 weeks has showed significant reduction in the side of vitamin C ($p = 0.002$), compared to the control side ($p = 0.142$).

CHEMICAL PEELINGS

Glycolide Acid

Erbil 2007[39]: a comparative, randomized and open study in 28 patients divided into 2 groups. Group 1: Cream of AZ 20% twice a day + adapalene 0.1% gel at night combined with 8 weekly sessions of peeling with glycolic acid 50-70% for 20 weeks. Group 2: AZ 20% twice a day + adapalene 0.1% gel at night. The assessment of the reduction of MASI showed 83.08% ($p = 0.001$) in group 1 and 69.34% ($p = 0.005$) in group 2.

Hurley, 2002[40]: Comparative, split-face and randomized study in 21 Hispanic women. They were submitted to 4 sessions of glycolic acid peeling of 20-30% for 15 days hemiface, associated with the use of HQ 4% cream twice a day. There was a significant decrease of melasma in both treatments ($p<0.01$) but not significant between hemifaces ($p = 0.75$).

Lim 1997[41]: Comparative, split-face and blind study in 10 Asian women, submitted to 8 sessions of peeling with glycolic acid 20-70% on a hemiface every 3 weeks, in addition to the use of glycolic acid 10% + HQ 2% across the face twice a day. The side that received the glycolic acid peeling obtained better results, but without statistical difference between the two sides ($p>0.059$).

Sarkar 2002[42]: A comparative, randomized and blinded study in 40 Indian patients, divided into 2 groups. A control group made daily use of modified Kligman's formula (tretinoin 0.05% + HQ 2% + hydrocortisone acetate 1%) versus the group that received 6 sessions of glycolic acid peeling, with an interval of 3 weeks, associated with daily use of the same formula. A significant reduction in MASI was observed in both groups ($p<0.001$). The peeling of the group has showed a trend of greater and more rapid

Rendon 2008[43]: A comparative, randomized and open study in 20 patients with moderate to severe melasma of the triple combination (of fluocinolona acetonide 0.01% + HQ 4% + tretinoin 0.05% in cream) versus serial glycolide acid peelings. Participants were treated with TC cream for 2 weeks before treatment. A total of six cycles of 2 weeks of alternating cream combined with 5 glycolic acid peelings were used. After 12 weeks, there was significant improvement in hyperpigmentation objectively assessed by spectrometry improvement ($p<0.001$).

Garg 2008[44]: A comparative, randomized and single-blind study in 60 patients divided into three groups. Group 1: glycolic acid peeling, without prior preparation of the skin, the groups 2 and 3 pre-peeling preparation made with retinoic acid 0.025% and HQ 2%, respectively, applied at night 2 weeks before the procedure. The initial concentration of glycolic acid was 20% and was increased 5% for each application. The assessment by MASI demonstrated in group 1 a decrease from 35.04% in 3 months, 29.85% in 6 months, both statistically significant ($p<0.001$) and decrease of 10.78% in 9 months, not significant. In group 2, there was decrease of 40.79%, 38.28% and 26.04% respectively ($p<0.001$). In group 3, there was decrease of 48.85%, 51.87% and 44.29% ($p<0.001$)

Jessner Solution X Salicylic Acid

Ejaz 2008[45]: A comparative, randomized and double-blind study in 60 Asian women divided into 2 groups. Group A was treated with Jessner solution peeling, and group B with salicylic acid 30% peeling, biweekly for 12 weeks. There was a statistically significant improvement in both groups ($p<0.0001$), but without statistical difference between them.

Jessner Solution X Glycolide Acid

Lawrence 1997[46]: Comparative, split face, randomized and open study in 16 women peeling using 70% glycolic acid versus Jessner solution in 3 sessions with monthly intervals. There was a decrease in the MASI of 63%, but without statistically significant differences between groups.

Trichloroacetic Acid (TCA)

Nanda 2004[47]: comparative, randomized and open study from 50 patients divided into 2 groups. For the preparation of the skin, group 1 has used HQ2 5% and Group 2 has used tretinoin 0.025% for 2 weeks prior to the serial peelings of ATA 10-30%, 6 sessions from 15 to 15 days. Group 1 has achieved better results in reducing the melasma and the maintenance of response ($p<0.05\%$).

Soliman 2007[48]: a comparative, randomized and open study in 30 women with epidermal melasma, divided into 2 groups. All the patients has used tretinoin gel 0.05% and HQ 4% once a day for 2 weeks before the weekly peelings of ATA 20% to total clearance or a maximum of 6 sessions. In a group, ascorbic acid was added 5% topical once a day to prepare, among peelings and weekly during the 16 weeks of follow-up. Evaluation by MASI, photos and opinion of the patient has showed that the combined treatment of ascorbic

acid in peelings of ATA 20% had better results and helped in the maintenance of therapeutic response.

Retinoic acid X Glycolide

Khunger 2004[49]: Comparative and split face study in 10 Indian women. A peeling of retinoic acid 1% was applied in a hemiface and on another, the glycolic acid 70%, weekly for 12 weeks. A significant decrease in MASI was observed on both sides ($p<0.001$), but without statistical difference between the two sides.

Lactide Acid X Jessner Solution

Sharquire 2006[50]: Comparative, split-face, non-randomized and single-blind study in 30 patients using peeling of lactic acid 92% on left hemiface and Jessner solution peeling on right hemiface, from 2 to 5 sessions every 3 weeks. After 6 months of the last session, there was reduction of MASI 79.34% with the use of lactic acid ($p<0.05$) and 80.26% with the use of Jessner solution ($p<0.05$), equating the effectiveness of the two agents.

Microdermabrasion

Bhalla 2006[51]: A comparative, randomized and open study in 30 patients, 10 with scarring from acne, 10 with melasma and 10 with photoaging. They were divided into 2 subgroups. Group 1 has performed microdermabrasion once per week for 6 weeks, group 2 has performed MDA and preparation of the skin with adapalene 0.1%, once a day for 2 weeks, started 2 weeks before MDA and maintained by 6 weeks. Subjective evaluation by patients and objectively by researchers has showed improvement in only 15% of patients in Group I of melasma, and 30 to 40% improvement in subgroup II of melasma.

Cotellessa 2003[52]: A comparative, not randomized and open study in 40 women divided into 2 groups. Group 1: MDA every 15 weeks and group 2: MDA + ATA 15% peeling every 3 weeks. In group 1, a complete remission was observed in 40% of patients, partial remission in 50% and no improvement in 10% after 8 sessions. After the following 2 to 4 months, the reappearance of new lesions occurred in 25% of patients with previous complete remission. In group 2, there was complete remission of 50% of patients, partial remission in 40% of patients and no improvement in 10% of patients. After the following 2 to 4 months, recurrence of lesions occurred in 50% of patients with complete remission.

Intense Pulsed Light (LPL)

Wang 2004[53]: A controlled, randomized and open study in 33 women with refractory melasma to the use of HQ, divided into 2 groups. Group 1: IPL, 4 sessions at monthly intervals. HQ and FPS were used during the study. Group 2: only HQ and FPS. After the 1st session, the MASI has showed reduction in 24% ($p<0.05$); after 16 weeks 39.8% ($p<0.005$) in group 1 and 11.6% in group 2. Group 1 was followed by a further 24 weeks, showing decrease in MASI of 24.2% over the original.

LASER

Angsuwarangsee 2003[54]: Comparative, split face and open study in 6 women with refractory melasma. On a hemiface, CO2 950-ms laser was used, 1 past followed by a past of Q-switched alexandrite laser 755 nm (QSAL). On the other hemiface only QSAL was used. After 6 months, the side with combined treatment has showed statistically significant reduction of M Case Report and Review of the Literature ASI and Mami ($p = 0.0238$ and 0.0223), however, on the side treated only with QSAL, there was no significant reduction.

ANALYSIS OF RESULTS AND CONCLUSION:

The studies have showed that the use of broad spectrum sunscreen, UVA and UVB [13,14] associated with bleaching creams is the fundamental basis for the treatment of melasma. The hydroquinone has showed as the most effective and safe isolated agent and with few adverse effects, both in treatment and in preparation of the skin to physical or chemical peelings[15,40,42-44,47-48,53]. The isolated use of retinoic acid is able to reduce the melasma but in high concentrations, it can cause undesirable results.[16-18] The effect of hydroquinone and retinoic acid is aggravated when used in combination with corticosteroids, demonstrating greater efficiency and lower total cost of treatment.[19-23] In addition to this well established classic combination, other agents such as azelaic acid[28,30,39], glycolic acid[25-27], skin whitening complex[32], liquiritin[37], rucinol[34], Niacinamide[35,36], KOJIC acid[26,27], vitamin C[15,25,31,38], Amelan[33], MELA D[33] and linoleic acid[29] have showed good results, either as active or supporting cast of other bleaching substances. However, neither of them clinically obtained the same power of hydroquinone bleaching but they had fewer adverse effects. Although the use of chemical peelings sessions or microdermabrasion can contribute to a faster response, the peelings of glycolic acid and Jessner solution were the most studied and with more positive results.[39-52]

Treatment with intense pulsed light[53] and laser[54] must be made with caution. Further studies using these methods should be performed, since the majority of published papers has presented inadequate methodology and / or very small number of participants. It is interesting to emphasize the use of new substances such as topic zinc sulphate 10%[55], ellagic acid[56], arbutin[56], pidobenzona 4%[57], methimazole[58], beta carotene[59], peeling of pyruvic acid 50%[60], oral pycnogenol[61],

intradermic tranexamic acid[62] and photodynamic therapy[63] with efficacy and safety not well established.

Regarding the methodology, there was a predominance of subjective methods (patient and observer opinions, photographic analysis) and quantitative (MASI and MAMI) for the effectiveness of the analysis. Few studies have performed a histological analysis. Given these results it can be concluded that combining topical agents such as HQ, tretinoin and a corticosteroid and educate patients regarding sun exposure and regular use of solar filter are still the pillars of the treatment of melasma. Although the literature is extensive and constantly updated and reviewed, the evidence of effectiveness, especially for new substances and less used is limited, and some controversies persist for heterogeneity and lack of well designed studies and impact. S&CD

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