Evidence-based Review, Grade of Recommendation, and Suggested Treatment Recommendations for Melasma

Abstract

Treatment of melasma is known to be less satisfactory, often incomplete, and relapse is frequent. Although many treatment options are available, they are either known to be unsafe on long-term use or their long-term safety profile is unknown. Patients often use various drugs, even topical steroid-based preparation without any medical supervision for long period of time, making the skin unsuitable for many of the drugs available. Thus, there has been gross disparity among the treating physician about what drugs and what regimen are best suitable for various categories of melasma patients and in different situations. With this background, numerous newer drugs, mostly combinations of some proprietary molecules or even unknown plant extracts, have flooded the market for the management of melasma. Information on efficacy or safety of these products are almost unknown. Studies on Asian people, especially Indian population, are far less commonly available. Therapeutic guideline for use on Indian patients with melasma is almost missing. Extrapolation of data from Caucasian people for use on Asian people may not be scientifically justifiable because Caucasian and Asian people are known to have inherent difference in their response as well as tolerance to the drugs used for melasma. With this background, we have extensively evaluated, following a strict, scientifically designed protocol, all the available studies on melasma management till May 2016 and prepared this document on level of evidence, grade of recommendation and suggested therapeutic guideline for melasma as per the method proposed by Oxford Centre of Evidence-Based Medicine. Various ethical, social, logical, regional, and economic issues in the context of Indian and similar populations were given due importance while preparing the suggested therapeutic recommendation.

Keywords: *Guideline, hydroquinone, India, melasma, treatment, triple combination*

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Introduction

Melasma is a common disorder characterized with brown, dark brown to grey pigmentation most commonly on face and sometimes on extra-facial areas such as forearm. Although no systemic involvement is known for this condition, it imparts significant psychological stress on the affected individual. Females are more commonly affected and seek treatment. Various aggravating and precipitating conditions are known to be related, but none has been proven. Hormonal factors, pregnancy, oral contraceptive pills are frequently reported to be intimately associated. Sun exposure, like all pigmentation, aggravates the intensity of pigmentation.

Numerous newer drugs, mostly combinations containing some proprietary molecules and unknown plant extracts, have flooded the market for the management of melasma. This has happened with the background that well-designed studies and thus documented information are lacking on the efficacy, safety, and right dosage on both the age-old drugs that are in use for significantly long time.

Treatment of this condition is less satisfactory. Relapse is frequent. Thus, a requirement for long-term therapy is often required. Unfortunately, most of the drugs with known good efficacy have some adverse effects (AEs) on skin on long-term use, limiting their use beyond a period. Thus, there has been gross disparity among the treating physician about what drugs and what regimen are best suitable for various categories of melasma patients and in different situations.

Studies on Asian people, especially Indian population, are far less commonly available. Therapeutic guideline for use on Indian patients with melasma is almost missing.

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Extrapolation of data from Caucasian people for use on Asian people may not be scientifically justifiable because Caucasian and Asian people are known to have inherent difference in their response as well as tolerance to the drugs used for melasma. This project was undertaken by "IADVL-Special Interest Group (SIG)—Pigmentary Disorders (2014–16)." Members outside the group were also included. The team was headed by the SIG coordinator (NS). Two face-to-face meeting among the SIG members were arranged; one at the beginning and another during the study, to discuss various aspects such as the search strategies, methodology for evaluation of the literature, preparation of evidence, and grading of recommendation. The project was approved by the IADVL Academy.

Objective

Preparing a scientifically designed, exhaustive document on level of evidence, grade of recommendation, and suggested therapeutic guideline for melasma.

Search period

Relevant articles on management of melasma published from January 2000 to May 2016.

Search strategy and inclusion criteria

All types of literature, including meta-analysis, randomized and nonrandomized trials, case reports, and case series, published only in PubMed and Cochrane database in English language were evaluated.

While calculating total number of participants, reviews were not considered. This was to avoid duplication of data as many of the studies we evaluated were also evaluated by these reviews.

Searches were made using the keyword "melasma."

Exclusion criteria

Studies were excluded if they were found to have the following: poor methodology and study design, unknown composition of the drug, unpublished studies and personal opinion, and when full text is unavailable. Studies using a combination molecule [additional molecules along with the intended single or combination molecules, e.g. triple combination (TC)] were also excluded.

Sponsored trials were, however, evaluated and categorized based on the study quality and methodology. Detailed information is presented later under individual drugs.

Level of evidence

Level of evidence (LOE) assessed as per "Oxford Centre for Evidence-Based Medicine (OCEBM) 2011."[1]

Grade of recommendation

Grading of recommendation was done based on OCEBM—Levels of Evidence (March 2009).[2]

Therapeutic guideline

This is a proposal and has been made by the present study team based on level of evidence, grade of recommendation along with consideration of various practical and ethical issues.

Assessment of study parameters

The following parameters were checked in the citations: number of patients, origin of the patients, study modality, study design, duration of study and follow-up, methods used for evaluation, AEs, any obvious fallacies, and other important facts.

Study team unanimously decided to consider following evaluation methods as standard: melasma area severity score (MASI), modified MASI (mMASI), and mexameter.

Limitations

Some new data might be published since the preparation of this article.

Detailed evidence on each drugs and grade of recommendation

Triple combination

Nineteen studies and one Cochrane review were found on TC.[3-22] Among these, 14 studies including one review were done with fluocinolone acetonide-based triple combination (FTC) monotherapy,[3-16] 3 used TC combined with other drugs[17-19] among which one study used hydrocortisone-based TC. Safety, risk of relapse, and efficacy of longer duration (6 months or longer) FTC were also assessed.[4,5,14-16] Four studies used TC with steroids other than fluocinolone acetonide.[19-22] Total number of patients evaluated with FTC (excluding the review) was more than 4000 patients [Table 1].

Fluocinolone acetonide-based triple combination monotherapy

FTC [fluocinolone acetonide (FA) 0.01%, hydroquinone (HQ) 4%, tretinoin (RA) 0.05%] was found to have significant efficacy in improving melasma in at least two uncontrolled trials (LOE 3).[3,4]

In comparison to placebo, FTC was found to be higher in efficacy in reduction of pigmentation in a study that also used sequential intense pulsed light (IPL) in both the groups (Goldman *et al.*)[7] (LOE 3). In other studies, FTC was found to be superior to 4% HQ monotherapy[8] (LOE 2), dual combinations (RA+HQ, RA+FA, and HQ+FA)[9] (LOE 2), and some proprietary skin lightening product (HQ-based combination product)[10] (LOE 2).

Our findings matched to the one published in 2010 by one Cochrane systematic review that evaluated 20 studies with a total of 2125 participants covering 23 different treatments.[12] It reported that TC cream was significantly more effective at lightening melasma than hydroquinone alone [relative

Table 1: Evidence on triple combination

Author name with year	Study type and level of evidence	Study modality	Patient profile	Result	Comments/ weakness
Rajaratnam *et al*.[12] (2010) (Cochrane)	Syst Rev LOE 1	Comparison of 23 different treatments	20 studies, 2125 participants	TC (tret + HQ + FA) significantly more effective at lightening melasma than HQ, tret + HQ, tret + FA, or HQ + FA	Gross heterogeneity of treatments in the reports Mild and transient AE is common
Arellano *et al*.[15] (2012)	RCT, SF, MC, B, LOE 2	Comparison of different schedule (twice weekly versus tapering regimen) of TC (FA 0.01%, HQ 4%, and RA 0.05%) Purpose: efficacy and safety Duration: 6 months Follow-up: nil Evaluation: GSS, MASI, MelasQol	320 patients (308 completed initial phase and 242 maintenance phase) Skin type III and IV	Twice weekly regimen more effective AE in 11% of cases (mostly mild, no serious AE)	
Hammami Ghorbel *et al*.[21] (2015)	RCT, SF, B, LOE 2	Copper bromide laser versus TC (HQ 5%, dexa 0.1%, and RA 0.1%) Duration: 3 mo Follow-up: 6 mo Evaluation: Subjective parameters, MASI	20 patients (16 completed) Skin type: II-IV Female: Male (F: M) = 5.6:1	TC more effective (*P*: 0.006)	Low sample size
Mahajan *et al*.[13] (2011)	RCT, DB, LOE 2	TC (HQ 2%, tret 0.05%, FA 0.01%) Versus GA peel (sequential increase from 20% till 70%) and azelaic acid (AA) 20% cream. GA peels repeated every 2 weeks and AA once daily Duration: 12 weeks Follow-up: 12 weeks Evaluation: MASI, Digital photography, VAS	40 Indian patients (38 completed) 20 in group A 18 in group B	Significant reduction in MASI from baseline Difference not significant among the two groups 4 patients in group A and 3 in group B experienced irritation, dryness, and photosensitivity	Combination therapy in the control arm
Monheit *et al*.[10] (2013)	RCT, SF, B, LOE 2	Skin lightening cream (combination of 4% HQ and 4 other substances) versus TC (4% HQ, 0.05% RA, and 0.01% FA) Duration: 12 weeks Follow-up: nil Evaluation: MASI	20 Caucasian females	Significant improvement in both but no significant difference between them (77% for SLC and 79% for TC cream)	Small sample size No follow-up

Contd...

Table 1: Contd...

Author name with year	Study type and level of evidence	Study modality	Patient profile	Result	Comments/ weakness
Pratchyapruit *et al*.[11] (2011)	RCT, SF LOE 2	TC versus TC (different steroid) (4% HQ, 0.05% RA, 0.01% FA) versus (4% HQ, 0.02% triamciniolone acetonide in hydrophilic cream, 0.05% tretinoin cream) Duration: 8 weeks Follow-up: 40 weeks Evaluation: Mexameter	40 Thai women Skin type: IV and V All previously untreated 30 completed	Similar improvement in both groups	Small sample size
Chan *et al*.[8] (2008)	RCT, MC, LOE 2	FA 0.01%, HQ 4%, RA 0.05% versus HQ 4% Duration: 8 weeks Follow-up: nil Evaluation: GSS, MASI	260 Asian patients Female: Male (F: M): 20:1 Asian	TC more effective	No follow-up
Taylor *et al*.[9] (2003)	RCT, MC, B, LOE 2	RA 0.05% + HQ 4% + FA 0.01% versus dual: combinations (RA+HQ, RA+FA, HQ+FA) Duration: 8 weeks Follow-up: Nil Evaluation: Global assessment	641 (predominantly women) Skin types: I-IV	TC more effective than dual-combination agents	No follow-up Evaluation not standard
Chaudhary *et al*.[19] (2013)	Nonrandomized prospective comparative trial, LOE 3	TC versus TC with serial glycolic acid peeling TC=2% HQ, 1% hydrocortisone, and 0.05% RA Duration: 24 weeks Follow-up: nil Evaluation: MASI	20 patients in each group Indian	Combination: early and greater improvement	No follow-up
Goldman *et al*.[7] (2011)	Open, nonrandomized, SF, LOE 3	TC (RA 0.05% + HQ 4% + FA 0.01%) with sequential IPL versus control cream with sequential IPL Duration: 10 weeks Follow-up: nil Evaluation: MASI	56 patients All female Skin type: III and IV	TC cream with IPL more effective	No follow-up
Grimes *et al*.[3] (2006)	Open, MC, uncontrolled LOE 3	Efficacy of TC (RA 0.05%, HQ 4.0%, FA 0.01%) Duration: 8 weeks Follow-up: No follow-up Evaluation: MASI	1290 patients (1042 completed) Diverse race Fitzpatrick skin types: I-VI	Significant improvement	Short duration of study and no follow-up

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Table 1: Contd...

Author name with year	Study type and level of evidence	Study modality	Patient profile	Result	Comments/ weakness
Grimes *et al*.[14] (2010)	Open, nonrandomized LOE 3	Three different cohorts compared for different continuous and maintenance therapy regimens, each with TC (HQ 4%, RA 0.05%, and FA 0.01%) Duration: 24 weeks Follow-up: nil Evaluation: MASI	70 (52 completed) F: M: 51:1	Continuous daily treatment for 24 weeks was better than starting a maintenance after 12 weeks	Nonrandomized study No follow-up
Godse *et al*.[17] (2009)	Nonrandomized, comparative LOE 3	TC (2% HQ, 0.05% RA, and 0.01% FA) with GA peels, versus inactive cold cream Duration: not mentioned Follow-up: not mentioned Evaluation: Melanin pigment intensity scale and photographic evaluation	20 (18 Completed) F: M: 4:1 All Indian	Improvement in 50% (5/10) of patients. Two patients showed more than 75% improvement	Many important information missing Evaluation: not standard Indian study
Rendon *et al*.[18] (2008)	Pilot study, Uncontrolled, LOE 3	Sequential treatment with TC (FA 0.01%, HQ 4%, and RA 0.05%) and a series of GA peels Duration: 12 weeks Follow-up: Evaluation: Skin pigmentation Analyzer® SPA 99	20 patients F: M: 19:1 Skin type: II-VI	More than 90% participants showed improvement	Evaluation: not standard Small sample size
Cestari *et al*.[4] (2007)	Open, MC, nonrandomized uncontrolled LOE 3	To validate the Brazilian Portuguese version of the MelasQoL evaluation questionnaire for patients with melasma (MelasQoL-BP) and to assess the impact of treatment with a TC cream (FA 0.01%, HQ 4%, and RA 0.05%) Duration: 8 weeks Follow-up: nil Evaluation: MelasQoL	300 patients Most had skin phototype type IV (Indian skin type)	Good or excellent results in 91.4% of the patients. Significant reduction on MelasQoL-BP scores	No follow-up Evaluation not standard
Torok *et al*.[6] (2005)	Open, MC, uncontrolled LOE 3	12-month extension of a randomized, investigator-blinded, multicenter, trial with TC (FA 0.01%, HQ 4%, RA 0.05%) cream Purpose: to see safety and efficacy of triple combination Duration: 12 months Follow-up: nil Evaluation: global assessment	569 patients (327 completed)	80% of patients had complete/ near complete improvement Adverse effects were noted	Evaluation: not standard No follow-up

Contd...

Table 1: Contd...

Author name with year	Study type and level of evidence	Study modality	Patient profile	Result	Comments/ weakness
Torok *et al.*[5] (2005)	Open, MC, uncontrolled LOE 3	TC (FA 0.01%, HQ 4%, RA 0.05%) Purpose: To see safety and efficacy of triple combination Duration: 12 mo Follow-up: nil Evaluation: global assessment	228 patients (173 completed) F: M: 37:1 Skin type: I-IV	92.3% of patients had completely or nearly cleared lesions 129 (57%) patients experienced treatment-related AEs	Evaluation: not standard No follow-up
Majid[20] (2010)	Case controlled observational study LOE 4	TC (Mometasone 0.1%, 2% HQ, and 0.025% RA) Purpose: safety of the mometasone-based TC Duration: 1 year Follow-up: nil Evaluation: questionnaire-based	60 patients Indian F: M=3.3:1	AE was seen in 26 patients (43.3%)	Evaluation methods: not standard
Hexsel *et al.*[16] (2014)	RCT, LOE 2	Comparison of two regimens of TC (FA 0.01%, HQ 4%, RA 0.05%) Duration: 6 mo Follow-up: nil Evaluation: Mexameter, MASI	20 patients (16 completed) Brazilian patients	Twice weekly regimen and tapering regimen resulted in similar result	

Syst Rev: Systematic review, RCT: Randomized controlled trial, SF: Split face, MC: Multicentre, B: Blind

risk (RR) 1.58, 95% confidence interval (CI) 1.26–1.97], dual combinations of tretinoin and hydroquinone (RR 2.75, 95% CI 1.59–4.74), tretinoin and fluocinolone acetonide (RR 14.00, 95% CI 4.43–44.25), or hydroquinone and fluocinolone acetonide (RR 10.50, 95% CI 3.85–28.60).

A subsequent Indian study, however, found FTC to be of equal efficacy to a combination therapy that consisted of glycolic acid (GA) peel (sequentially increased from 20 to 70%) along with azelaic acid 20% cream[12] (LOE 2). More studies are necessary to substantiate this finding.

Recommendation

1. *FA-based TC (FA 0.01%, HQ 4%, RA 0.05%) is recommended in melasma (Grade A recommendation)*
2. *FA-based TC (FA 0.01%, HQ 4%, RA 0.05%) is preferable to all other mono and combination topical therapy when potency of the therapy is the priority. This is a typical situation at the initiation of therapy for a short period (Grade A recommendation).*

Triple combination in combination therapy

Three studies evaluated TC in combination with other drugs.[17-19] TC combined with GA peel was reported to be efficacious (LOE 3)[17,18] but magnitude of the benefit of additional GA peel in comparison to TC alone was not studied. In a small nonrandomized study, additional benefit of GA peel on hydrocortisone containing TC (hydrocortisone 1%, HQ 2%, and RA 0.05%) was assessed.[19] Authors found greater and early improvement with combination treatment (TC and GA peel) (LOE 3).

Recommendation

GA peel can be added to TC to increase the efficacy (Grade of recommendation B).

Duration of therapy (initial therapy phase)

Most of the studies have evaluated TC up to a maximum of 8–12 weeks. There is inconsistencies and significant lack of proper reporting of AE in these studies. Thus, it is difficult to conclusively recommend the most safe and effective duration.

Recommendation

- *Initial daily therapy with FB TC should be limited to 8 weeks. However, this may be extended carefully up to 12 weeks (Grade of recommendation D).*

Long-term therapy with triple combination

Relapse was noted among almost all cases who improved after treatment for 12 weeks (LOE 3). This called for reinstitution of daily therapy.[14]

Another study, however, noted a longer disease-free period during 6 months of intermittent maintenance therapy after initial 8 weeks of daily therapy. It was reported that 53% of patients remained relapse-free with improved quality of life with median time to melasma relapse as 190 days and it was similar between the groups[15] (LOE 2).

Studies have used daily[4] as well as intermittent regimens[5,14-16] with TC for extended period (6 months to 1 year). Common AEs were erythema and skin irritation. Incidence of significant AE such as skin atrophy, telangiectasia was reported to be very low in all these studies. No incidence of exogenous ochronosis was detected in any of these long-term studies. Withdrawal due to AE was also very low.

High degree of safety was reported after 12 months daily use of FTC[4] (LOE 3). However, in contrast to intermittent therapy, one study reported significantly higher incidence of AE when TC was used daily as long-term therapy[14] (LOE 3).

Among the two intermittent regimens (twice weekly versus tapering dose) up to 6 months, there was no significant difference between efficacy in maintaining a disease-free period and the risk of AE[15,16] (LOE 2). However, none of the studies were done among Indian population. Chance of AE among Asians is often reported to be higher than Caucasians.

Recommendation

- *Till further evidence on Indian population is available, long-term use of TC as maintenance therapy is not recommended (Grade of recommendation D)*
- *If used, FTC may be used as twice weekly maintenance therapy very carefully under supervision up to 6 months (Grade of recommendation A).*

Triple combination using steroids other than fluocinolone acetonide

AEs were noticed among 43.3% patients in one retrospective study that used mometasone containing TC (mometasone 0.1%, 2% HQ, and 0.025% RA) for one year. Steroid-induced telangiectasia was the commonest finding. Atrophy, hypertrichosis, and acneiform eruption were also seen[20] (LOE 4).

Only one study was found that compared FA and triamcinolone (0.02%) containing TC. Both were found to be similar in efficacy[21] (LOE 2). Difference in AE was also not reported. Follow-up was missing in many of these studies. Thus, comparative risk of relapse or AE is unknown.

One recent study compared dexamethasone containing TC (original Kligman's formula, dexamethasone acetate 0.1%, HQ 5%, and RA 0.1%) with copper bromide laser and reported this TC to be better than laser[21] (LOE 2). However, sample size was very less (only 16 patients completed the trial).

Recommendation

There is significant lack of evidence on TC using steroids other that fluocinolone acetonide-based TC (FTC). Thus, despite lack of direct comparative study between FTC and TC containing other steroids, FTC is preferable as TC (Grade of recommendation D).

Hydroquinone

Evidence

The literature search yielded 122 citations using the key phrase topical hydroquinone in melasma. The articles which were excluded had poor methodology of evaluation. Few studies were excluded as full text were not available. Finally, 11 studies, including 9 randomized controlled trials (RCTs), were evaluated that used 4% HQ among 735 subjects[22-33] [Table 2].

HQ 4% was found to be more effective than placebo in the treatment of melasma.[22,23] In addition, HQ 4% was reported to be significantly superior to 5% ascorbic acid[24] (LOE 2). Although 4% HQ resulted in higher efficacy than kojic acid (0.75%)[25] (LOE 3) and 4% niacinamide[26] (LOE 2), difference was not statistically significant.

One Cochrane review reported azelaic acid (20%) was superior to HQ 2% but not when compared to 4% hydroquinone (RR 1.11, 95% CI 0.94–1.32)[12] (LOE 1). Since that review was published, only one study reported 20% AA as significantly more efficacious than 4% HQ[27] (LOE 3).

A single study reported lesser efficacy when compared to 3% rumex occidentalis[28] (LOE-2) and 1% flutamide[29] (LOE-2). No further studies substantiated these findings however. All the three RCTs comparing efficacy of 4% HQ with TC (two fluocinolone-based[8,32] and one dexamethasone-based[33]) confirmed significantly superior efficacy of TC (LOE 2). However, posttreatment follow-up data beyond 12 weeks of therapy was not available.

Pigment lightening effect of HQ is mostly evident after 8–12 weeks.[22,23] Some studies have continued till 24 weeks without any report of AE.[27,28] None of the studies included dermal melasma in study subjects.

Irritation is the main AE with HQ.[22,23,26] Overall, reporting of AE appeared to be lower than expected. No report of exogenous ochronosis was reported with 4% HQ on using it more than 3 months.

Conclusion and recommendation

HQ 4% is a known effective drug in melasma. Considering its long track record of use and satisfactory efficacy, the evidence appears grossly lacking.

Table 2: Evidence on hydroquinone

Authors	Study, type and LOE	Treatment mode	Patient profile	Results	Comments/ weakness
Ennes *et al*.[23] (2000)	R, DB LOE 2	4% HQ versus placebo Duration: 12 weeks Follow-up: nil Evaluation: clinical and photographic documentation	48 patients Fitzpatrick skin type IV and V	HQ was significantly efficacious than placebo 3 patients discontinued due to AE	Evaluation parameters not standard
Haddad[22] (2003)	R, DB, SF LOE 2	Two different cohorts Group 1: 4% HQ + placebo Group 2: Proprietary 5% skin lightening cream (SPF 25) versus placebo Duration: 3 months Follow-up not available Evaluation: Unknown	30 patients Fitzpatrick skin type: IV-VI	HQ showed more efficacy but difference not significant AE: irritation in HQ group but not statistically significant	Follow-up not available Comparison between the proprietary product and HQ not assessed Evaluation parameter not mentioned
Farshi *et al*.[27] (2011)	R, open trial LOE 2	4% HQ versus azelaic acid 20% Duration: 8 weeks Follow-up: nil Evaluation: MASI	29 patients from Middle-East Mild melasma	20% AA significantly better than 4% HQ	Small sample size No follow-up
Espinal-Perez *et al*.[24] (2004)	R, DB LOE 2	4% HQ versus 5% ascorbic acid Duration: 16 weeks Follow-up: Unknown Evaluation parameters: subjective, colorimetry, digital photography, and regular color slides	16 women Mexican	Statistically significant improvement with 4% HQ More AE (68.7% versus 6%) in HQ than ascorbic acid	Low study population Evaluation: not standard
Mendoza *et al*.[28] (2014)	R, DB, placebo-controlled LOE 2	3% Rumex Occidentalis cream (RO) versus 4% HQ Duration: 8 weeks Follow-up: Unknown Evaluation: MASI, Mexameter	45 subjects Skin type: IV Epidermal and mixed melasma	RO greater improvement than the HQ	
Navarrete-Solis *et al*.[26] (2011)	R, DB, split-face LOE 2	4% Niacinamide versus 4% HQ Duration: 8 weeks Follow-up: Unknown Evaluation: subjective scales and histological sections	27 subjects	Both the treatments were effective (No statistical difference) AE: 18% with niacinamide versus 29% with HQ	Low study population No data on follow-up Evaluation: not standard
Adalatkhah *et al*.[29] (2015)	R, DB LOE 2	HQ 4% cream versus 1% flutamide cream Duration: 16 weeks Follow-up: not available Evaluation: MASI mexameter	74 subjects All women	16 weeks Result: Better treatment efficacy-based on MASI scale for flutamide group compared to the hydroquinone group (P<0.05) but no significant difference in mexameter scores	New study first of its kind. Needs more evidence for validation

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Table 2: Contd...

Authors	Study, type and LOE	Treatment mode	Patient profile	Results	Comments/ weakness
Astaneh *et al*.[31] (2005)	RCT, DB LOE 2	4% HQ versus 4% HQ, 0.05% tret, and 0.05% dexamethasone Duration: 12 weeks Follow-up: nil Evaluation-rating scale evaluating the darkness of melasma and lesion size	64 patients Skin type III to V	Significant reduction in combination group	Posttreatment follow-up not available Evaluation: not standard
Chan *et al*.[8] (2008)	RCT, SB, Multicentric 2	4% HQ versus TC (retinoic acid 0.05% + 4% HQ + fluocinolone 0.01%) Duration: 8 weeks Follow-up: nil Evaluation: MASI, global severity assessment, global improvement, and patient satisfaction	222 Asian subjects, moderate to severe melasma	Significantly higher improvement with TC than HQ	No posttreatment follow-up
Ferreira *et al*.[30] (2007)	R, O 3	HQ 4% versus TC (retinoic acid 0.05% + 4% HQ + fluocinolone 0.01%) Study duration: 8 weeks Evaluation: global severity assessment, improvement of melasma over time	120 subjects	Significantly higher improvement with TC than HQ AE (erythema, burning, and desquamation) similar in both groups	Type of subjects not mentioned Posttreatment follow-up not available
Monteiro *et al*.[25] (2013)	Open, NR 3	4% HQ versus 0.75% kojic acid Study duration: 3 months Additional follow-up: nil Evaluation parameter: MASI	60 subjects Indian	4% HQ better compared to 0.75% KA	Follow-up available
Gold *et al*.[32] (2013)	Multicentric Open-label 3	4% HQ skin care system + 0.05% tret Proprietary ? Duration: 24 weeks Follow-up: nil Evaluation: melasma severity, melasma pigmentation intensity, melasma improvement, patient satisfaction, quality-of-life measure	37 patients with moderate or marked epidermal melasma Fitzpatrick skin type: III-VI	Significant reduction in pigment intensity from baseline	Proprietary product? Uncontrolled Evaluation method not standard
Grimes *et al*.[33] (2013)	Open label Single-center 3	4% HQ skin-care system + 0.025% tret Duration: 12 weeks Evaluation parameter: MASI and other methods	20 subjects Fitzpatrick skin type: III-VI	Significant reduction from baseline AE: Dryness, erythema, peeling, and stinging sensation in 3 patients	Small study subjects Noncomparative
Rendon *et al*.[34] (2016)	NR, blinded 3	4% HQ skin care system + 0.02% tret Duration: Unknown Follow-up: Unknown Evaluation parameter: MASI	39 subjects Fitzpatrick skin type: III-VI 24 weeks	Significant reduction in MASI at week 24	Noncomparative

Syst Rev: Systematic review, RCT: Randomized controlled trial, SF: Split face, MC: Multicentre, B: Blind, R: Randomized, DB: Double blind, SB: Single blind, O: Open trial, NR: Non randomized,

Evaluating the available studies, we recommend HQ 4% in melasma (Grade A recommendation).

The maximum recommended duration is 16 weeks. It is superior to many available therapies except TC, which proved to be more efficacious and azelaic acid 20%, which may be equal in efficacy.

Hydroquinone with tretinoin

Three uncontrolled studies evaluated efficacy of the 4% HQ with tretinoin (0.025–0.05%) mostly for 12–24 weeks [Table 3]. All these studies reported efficacy of such combination. However, all the three studies used proprietary product. AEs such as burning, irritation, redness, and dryness were reported (LOE 3).[34-36]

Recommendation

No recommendation possible unless further studies are available.

Retinoids

Evidence

Literature search yielded 94 articles. After primary screening, 90 articles were excluded as these used combination therapies. Finally, four articles were assessed, including one Cochrane systematic review[12,35-37] [Table 3].

Two studies used 0.1% RA (tretinoin) and the other one 0.05% isotretinoin gel.[35-37] Both tretinoin and isotretinoin were compared with vehicle, and the mask study was uncontrolled.

Improvement with tretinoin was higher than vehicle (LOE 2). Overall improvement in MASI (in one of these two) was only 32%.[36] Objective improvements in the studies were mentioned to be significant in both the studies. However, participants rated their improvement as significant in one study only.

These studies had many weaknesses. Sample size was too small. The largest one was done among 38 subjects. One study was not evaluated with standard assessment method such as MASI, and both these studies had no follow-up. Retinoid dermatitis was noted in large number of cases.

Topical isotretinoin was not found to be superior even to the vehicle. In an uncontrolled study on only 20 patients, retinoid mask was found to offer significant improvement in MASI from baseline and the improvement persisted during one year of follow-up.[37]

Table 3: Evidence on retinoids in melasma

Authors	Study details, type and LOE	Treatment modality	Patient profile	Result	Comments/weakness
Rajaratnam *et al*.[12] (2010)(Cochrane)	Syst. Rev	Comparison of 23 different treatments	20 studies, 2125 participants	TC (tret + HQ + FA) significantly more effective at lightening melasma than HQ, tret + HQ, tret + FA, or HQ + FA	Gross heterogeneity of treatments in the reports Mild and transient AE is common
Griffiths *et al*.[35] (1993)	Double-blind RCT LOE-2	0.1% RA versus vehicle cream Once daily application Duration: 40 weeks Follow-up: nil Evaluation parameter: colorimetric (mexameter) analysis and histology	38 female	13 (68%) of 19 RA treated patients were clinically rated as improved or much improved compared to 1 (5%) of 19 in the vehicle group	No follow-up
Kimbrough-Green *et al*.[36]	DB RCT LOE-2	0.1% RA (tretinoin) versus vehicle applied once daily Duration: 40 weeks No follow-up Evaluation: MASI, colorimetric analysis, and histology	30 patients (28 completed) Skin type: V and VI	MASI reduction by 32% in tretinoin treated group, 10% improvement in the vehicle group	Patient number less AE: Mild retinoid dermatitis in 67% of patients No follow-up data available
Leenutaphong *et al*.[37] (1992)	RCT LOE 2	0.05% Isotretinoin gel versus its vehicle base with a broad spectrum sunscreen (SPF 28) Duration: 40 weeks Follow-up: nil Evaluation: MASI, colorimeter (MAMI)	30 subjects with moderate to severe melasma	There was no significant difference between the isotretinoin gel and the control group, however, the MASI score declined significantly from baseline	Follow-up: nil Mild transient "retinoid dermatitis" in 27% of isotretinoin-treated patients

Syst Rev: Systematic review, RCT: Randomized controlled trial, DB: Double blind

Conclusion and Recommendation

Overall, the high-quality evidence is lacking in favor of retinoid monotherapy in melasma. Comparative studies with standard treatment options like TC or HQ are unavailable.

Retinoid monotherapy results in only mild improvement. It has known adverse effects also. It may be used in some selected cases of melasma (Grade B recommendation).

Vitamin C

Evidence

Twelve studies were sorted out where vitamin C was used in melasma. One study was excluded as it was done before 2000. Six other studies were excluded because of the weaknesses in study design. Finally, five studies matched the selection criteria[24,38-41] [Table 4]. Three studies evaluated vitamin C as monotherapy and compared with other modalities.[24,38,39]

Vitamin C was reported to be more efficacious than distilled water iontophoresis[38] (LOE 2). Also, vitamin C was found to result in higher improvement (statistically insignificant) than 70% GA peel. However, the study was done only among 14 patients and follow-up was missing[39] (LOE 2).

It was, however, found to be inferior to HQ 4%[24] (LOE 2).

Two studies found significant additional benefit of adding vitamin C to other modalities such as 20% trichloroacetic acid (TCA) peel[40] (LOE 3) and 1064-nm Q-switched Nd:YAG laser[41] (LOE 2). However, the latter study was done only on 8 patients and evaluated the response with VASI and the former study had a complex study design without any follow-up.

Recommendation

Vitamin C is an expensive drug. Stability is an issue. At present, there is insufficient evidence to recommend the drug either as monotherapy or as adjuvant. Larger studies are necessary to assess its efficacy.

Vitamin E

Evidence

Two studies used vitamin E in melasma.[42,43] None of these two studies used vitamin as monotherapy.

Table 4: Evidence on Vitamin C

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments
Lee *et al*.[41] (2015)	RCT, SF, LOE 2	1064 nm QS Nd: YAG monotherapy (4 sessions, monthly) versus laser and ultrasonic application of vitamin C Duration: 4 mo Follow-up: 3 mo Evaluation: visual analog score	8 patients, Age: 32-45 years (mean: 37 years)	Combination better	Assessment: not standard Small sample size
Huh *et al*.[38] (2003)	RCT double-blind placebo LOE 2	Vitamin C versus distilled water iontophoresis Duration: 8 weeks No follow-up Evaluation: colorimetric measurement	29 Female patients with melasma Mean age of 37.2 years	Vit. C was found better	Assessment: Not standard No follow-up
Espinal-Perez *et al*.[24] (2004)	RCT LOE 2	4% HQ versus 5% ascorbic acid 16 weeks study No follow-up Evaluation: patient's subjective response and colorimetric assessment	16 Females Mean age of 36 years	HQ better (patient's subjective assessment) and caused more as well as caused more irritation Colorimetric assessment showed no difference	
Soliman *et al*.[10] (2007)	Nonrandomized LOE 3	20% TCA peel versus 20% TCA peel + 5% ascorbic acid cream applied daily Duration: 16 weeks No follow-up Evaluation: MASI and other	30 women 2 equal groups Bilateral epidermal melasma Skin types III and IV	Combination significantly better	No follow-up
Sobhi *et al*.[39] (2012)	Single-blinded, split-face RCT LOE 2	Glycolic acid 70% versus nanosome vitamin C iontophoresis 6 sessions Duration: not mentioned Follow-up: not mentioned Evaluation: MASI and global evaluation	14 female (13 patients completed) Skin types IV and V: Mean age 39.36 years	Vitamin C fared better than glycolic acid	Duration of follow-up after sixth session not mentioned

RCT: Randomized controlled trial, SF: Split face

Recommendation

Presently, there is lack of evidence to recommend vitamin E as monotherapy in melasma.

Glycolic acid cream

Evidence

Most of the available studies on GA were done on the GA peel and has been mentioned somewhere else in this document. Only two studies were found that evaluated GA cream formulation[44,45] [Table 5].

Among these, one open label uncontrolled study used a novel proprietary synthetic oligopeptide cream also containing GA as one of the ingredient and reported complete clearance of melasma after 6 weeks.[44] Thus it was not rejected.

One RCT evaluated GA cream as an adjuvant to 4% HQ.[45] The study compared five groups where each group had 4% HQ and efficacy of additional drugs such as 10% GA and 0.01% hyaluronic acid was assessed. Efficacy of additional GA cream to HQ was not proven in this study (LOE 2).

Recommendation

There is lack of evidence to recommend use of glycolic acid cream in melasma.

Azelaic acid

Evidence

Seven studies including one systematic review (Cochrane review) were found to evaluate efficacy of azelaic acid in melasma.[12,27-29,52-56] Total patients evaluated were 383 (excluding the review) [Table 6].

One Cochrane review, published in 2010, reported equal efficacy of AA 20% to that of HQ 4%[12] (LOE 1). One RCT published after that review even reported higher efficacy of AA 20% than HQ 4% (LOE 2). However, the number of patients was only 29.[27]

That Cochrane systematic review reported significantly higher efficacy of AA 20% than HQ 2%[12] (LOE 1). No other study was found since 2000.

Combination of Nd:YAG laser with AA 20% cream was also found to be better than the laser monotherapy among 60 patients[49] (LOE 3).

No significant AEs were reported. Long-term AE is unknown. Thus, evidence is limited but suggests efficacy comparable to HQ 4% and short-term safety profile. Long-term safety of data is, however, lacking. More studies are required.

Recommendation

Azelaic acid 20% cream monotherapy is recommended in melasma (Recommendation Grade A).

Table 5: Evidence on glycolic acid cream

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments
Ibrahim *et al.*[45] (2015)	RCT LOE 2	Comparison between five groups Gr A: 4% HQ Gr B: 4% HQ + 10% GA Gr C: 4% HQ + 0.01% hyaluronic acid Gr D: 4% HQ + 10% GA + 0.01% hyaluronic acid Gr E: placebo Duration: 6 months Follow-up: nil Evaluation: mMASI and other dermoscopy	100 female patients 5 equal groups All females	All active groups significantly better than placebo HQ + GA was inferior to HQ + GA + HA and even to HQ monotherapy HQ+GA had more AE than other groups	
Hantash *et al.*[44] (2013)	Open-label trial, uncontrolled LOE 3	Evaluation of a novel proprietary synthetic oligopeptide (combination of a novel oligopeptide with glycolic acid and sunscreen) Duration: 16 weeks Follow-up: nil Evaluation: physician's global assessment	5 Female Fitzpatrick phototype IV and moderate Recalcitrant melasma	4 Patients showed complete clearance in 6 weeks	Evaluation: not standard Small sample size

RCT: Randomized controlled trial

Table 6: Evidence on azalaic acid

Author name with year	Type of study and level of evidence	Study Modality	Patient profile	Results	Comments/ weakness
Rajaratnam *et al*.[12] (2010) (Cochrane)	Syst Rev	Comparison of 23 different treatments	20 studies, 2125 participants	TC (tret + HQ + FA) significantly more effective at lightening melasma than HQ, tret + HQ, tret + FA, or HQ + FA	Gross heterogeneity of treatments in the reports Mild and transient AE is common
Verallo-Rowell *et al*.[48] (1989)	Double-blind RCT LOE 2	Azelaic acid (20%) versus 2% HQ Duration: 24 weeks Follow-up: 6 months	155 patients 146 female and 9 male	73% of the azelaic acid patients (compared with 19% of the hydroquinone patients) had good to excellent overall results	Assessment: not standard
Mazurek *et al*.[46] (2016)	Double-blind RCT LOE 2	Comparison of efficacy of three dermocosmetic products containing azelaic acid Duration: 6 mo study Follow-up: nil Evaluation: mexameter, corneometer, and reviscometer	60 women Aged 35-55 years	All dermocosmetics significantly reduced pigmentation	Assessment: not standard
Mahajan *et al*.[13] (2015)	RCT LOE 2	TC (HQ 2%, tretinoin 0.05%, fluocinolone 0.01%) versus combination of glycolic acid (GA) peels and azelaic acid (20%) cream Duration: 6 mo Follow-up: 3 mo Assessment: MASI	40 patients M: F=1:9	Both groups: same efficacy	
Sarkar *et al*.[47] (2002)	Nonrandomized single-blind, split-face comparative pilot study LOE 3	Azelaic acid cream 20% monotherapy versus a sequential therapy (clobetasol propionate 0.05% cream for 8 weeks followed by 20% AA cream for 12 weeks) Duration: 24 weeks No follow-up Evaluation: photography and the global efficacy	30 Indian patients 25 females, 5 males Ages ranged from 21 to 45 years	96.7% and 90% of patients of each group (sequential therapy and AA) had good to excellent responses to treatment	Assessment not standard
Bansal *et al*.[49] (2012)	Open label comparative study LOE 3	Low-fluence 1064-nm Q-switched Nd: YAG laser monotherapy versus 20% azelaic acid cream monotherapy versus their combination Duration: 12 weeks 10 passes of laser at weekly intervals No follow-up Evaluation: MASI	60 patients (20 in each group) 59 females, 1 male Indian	Significant improvement was recorded in all the three groups. Group C had statistically highly significant improvement compared to group A Combination was better than either treatment alone and statistically significant when compared with laser alone	
Farshi *et al*.[27] (2011)	Open label, nonrandomized LOE 3	Azelaic acid (20%) cream versus 4% HQ cream Duration: 2 months Follow-up: No follow-up evaluation by MASI	All 29 were women. 15 in HQ arm and 14 in azelaic acid arm	20% azelaic acid cream is more effective than hydroquinone 4% in reducing mild melasma	

Syst Rev: Systematic review, RCT: Randomized controlled trial

Azelaic acid 20% cream is recommended as adjuvant to Nd:YAG laser therapy in melasma (Recommendation Grade B).

Arbutin

Evidence

Four studies were found that evaluated arbutin in melasma[50-53] [Table 7]. In two studies, arbutin was used either in a proprietary cream that also had other drugs or along with Nd:YAG laser. These were thus excluded.[50,51]

One study (54 melasma patents, 8 weeks) compared arbutin with a placebo and reported statistically significant difference. However, evaluation was not done using a standard method[50] (LOE 2).

In another study, it was compared with two formulations of elagic acid. All the drugs were effective in significantly improving from baseline, but there was no difference among them[53] (LOE 2).

In summary, efficacy of arbutin is yet to be understood due to gross lack of high-quality comparative studies with standard drugs used in melasma. There is no data on the possible AE.

Recommendation

However, this may be used in melasma for short term. (Grade D recommendation).

Kojic acid

Evidence

Four RCTs were found on use of kojic acid (KA) in melasma. However, sample sizes were less, and strengths of KA were variable (0.75–2%)[25,54-56] [Table 8].

One RCT compared 2% KA with HQ 2% among 39 patients (only one male) in a split-face manner where both sides were also treated with 5% GA. There was no difference between the two drugs[54] (LOE 2).

Another study found KA (0.75%) (along with vitamin C, 2.5%) was inferior to 4% HQ that showed faster and significantly higher improvement in MASI[25] (LOE 2).

Study by Deo *et al.*[55] reported 58.72% improvement in MASI with 1% KA monotherapy and 71.87% response with combination of KA and 2% HQ (LOE 2).

Table 7: Evidence on arbutin

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Result	Comments/ weakness
Morag M *et al.*[52] (2015)	Randomized placebo-controlled LOE 2	2.51% of arbutin (Leaf extract) versus placebo Duration: 8 weeks Follow-up: nil Evaluation: videodermatoscope with a Mexametr® MX18 probe	102 women (melasma 54 and lentigo solaris 48) All patients are female	Statistically significant lightening	No follow-up
Ertam *et al.*[53] (2008)	Randomized controlled Level 2	Natural elagic acid versus synthetic elagic acid versus arbutin Duration: 6 mo Follow-up: nil Evaluation: clinical and mexameter	30 females	Significant improvement from baseline in all 3 No significant difference among them	
Crocco *et al.*[50] (2015)	Open label, uncontrolled, LOE 3	Combination of nicotinamide 4%, arbutin 3%, bisabolol 1%, and retinaldehyde 0.05% Duration: 60 days Follow-up: nil Evaluation: MASI	35 female Fitzpatrick skin types I-V	Significant improvement	Combination product No follow-up
Polnikorn[51] (2010)	Prospective , uncontrolled LOE 3	Q-switched Nd: YAG laser +7% alpha arbutin solution (1064 nm, 6-mm spot size, 3-3.4 Joules/cm^2, 10 Hz) Duration: 6 mo Follow-up: nil Evaluation: physician global response	35 female patients All resistant to hydroquinone cream or Kligman's formula	30% subjects - excellent clearance (>81% reduction) 36.7% good (51-80%) AE: 3 cases - mottling hypopigmentation	Evaluation not with standard method AE noted

Table 8: Evidence on kojic acid

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Lim[56] (1999)	Double-blind, RCT, split-face comparison, LOE 2	Combination with KA (2% HQ, 10% GA, 2% KA) versus combination without KA (2% HQ,10% GA) 12 weeks study, Follow-up: Unknown Evaluation: Unknown	40 Chinese (35 completed)	Only in 17 patients, KA side showed dramatic reduction	Evaluation: not standard
Monteiro *et al*.[25] (2013)	Double-blind, RCT LOE 2	4% HQ versus 0.75% kojic acid + 2.5% vitamin C Duration: 12 weeks No follow-up Evaluation by MASI	60 patients of both sexes	0.75% KA significantly poorer and slower than 4% HQ	KA monotherapy not assessed No follow-up
Deo *et al*.[55] (2013)	Single-blind RCT LOE 2	Comparison in four groups: Gr A: 1% KA Gr B: 1% KA + 2% HQ Gr C: 1% KA + 0.1% bet val Gr D: 1% KA 2% HQ + 0.1% bet val Duration: 12 weeks No follow-up Assessment: MASI	80 Indian patients 67 females and 13 males	Improvement - Gr A: 58.72%, Gr B: 71.87% (highest), Gr C: 36.46% (lowest), Gr D: 54.03%	

RCT: Randomized controlled trial

Role of additional KA (2%) over a combination therapy containing 2% HQ, 10% GA in another randomized single-blind 12-week study produced a mixed result. A dramatic reduction was reported among 17 patients but no additional benefit was found among other 18 patients. However, evaluation was not done using standard method such as MASI[56] (LOE 2).

In summary, studies are limited and there are heterogeneity in the available studies with KA. Most studies have used it along with other drugs. Combination with 2% HQ may offer highest possible benefit from this drug. It appears that 2% KA may have an efficacy similar to 2% HQ. Strength lower than 1% may not be effective. Larger and more designed studies are necessary to understand its true efficacy. Long-term safety of data is also largely lacking.

Recommendation

Kojic acid (preferably 2%) is recommended in melasma (LOE 2, Grade A recommendation).

This may be combined with 2% HQ for a better result (LOE 2, Grade A recommendation).

Chemical Peels

Glycolic acid

Evidence

Totally, 389 patients were assessed in nine studies including five RCTs[13,57-64] [Table 9]. Two studies compared efficacy of GA peel in variable percentages (20–70%) with other drugs. One of these studies compared efficacy of GA (20–70%) peel with TC (HQ 2%, RA 0.05%, FA 0.01%). Both GA peel (along with azelaic acid cream) and TC significantly improved MASI and there was no statistically significant difference in efficacy between them[13] (LOE 2). However, sample size was small. No other studies were done to validate these findings.

GA peel (70%) was found to be similar in efficacy with tretinoin 1% peel but tretinoin peel was more tolerable by the patients[57,58] (LOE 2, 4). Combining other drugs like HQ 2% or 0.25% tretinoin was found to be superior to GA peel alone in a RCT with small sample size (20 patients in each arm)[59] (LOE 2). It was a long duration study (6 months study and 3 months follow-up).

GA peel with HQ 2% was better than GA peel with 0.25% tretinoin.[59] In a small RCT involving 25 patients with recalcitrant melasma, the group receiving chemical peel along with topical 20% AA and 0.1% adapalene showed better response than the group receiving topical formulation alone[50] (LOE 2). However, in another small RCT, combining HQ 4% with GA peel was not found to be superior to HQ monotherapy[61] (LOE 2). Whether such combination was better than GA peel was, however, not studied.

In an open study, combining serial GA peel (30–40%) every 3 weeks with modified Kligmann formula for 21 weeks resulted in faster response, but overall efficacy was similar to TC alone[62] (LOE 3).

Table 9: Evidence on chemical peels in melasma

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Rajaratnam *et al*.[12] (2010) (Cochrane)	Syst Rev LOE 1	Comparison of 23 different treatments	20 studies, 2125 participants	TC (tret + HQ + FA) significantly more effective at lightening melasma than HQ, tret + HQ, tret + FA, or HQ + FA	Gross heterogeneity of treatments in the reports Mild and transient AE is common
Mahajan *et al*.[13] (2011)	RCT, double-blind LOE 2	TC (HQ2%, tret 0.05%, fluocino 0.01%) versus GA peel (sequential) and AA 20% Duration: 12 weeks Follow-up: 12 weeks Evaluation: MASI, digital photography, VAS	40 Indian patients (38 completed)	Significant reduction in MASI from baseline Difference not significant among the two groups	Efficacy of GA peel monotherapy cannot be evaluated Also this could only compare two incoherent groups
Faghihi *et al*.[57] (2011)	RCT, DB, split-face LOE 2	GA peel 70% versus tret 1% peel Four sessions at 2-week intervals Duration: 8 weeks Follow-up: nil Evaluation: MASI	63 subjects Male:female Origin	No significant difference between the groups Tretinoin 1% peels more tolerable	Follow-up missing
Garg *et al*.[59] (2008)	R, SB, LOE 2	Three groups of 20 patients each Gr A: 15 GA 20% →50%) Gr B: 17 0.025% tret + GA (20% →50%) Gr C: 18 2% HQ + GA (20% →50%) Duration: 6 mo Follow-up: 3 mo Evaluation: MASI	60 Indian patients with skin type IV 50 patients completed the course M: F=1:6.5 Mostly epidermal melasma	All group improved (Most significant in group C) Gr A>Gr B>Gr C	Primary target of this study was not to assess efficacy of GA peel but the efficacy of adding various adjuvant priming regimen with it
Erbil *et al*.[60] (2007)	RCT, LOE 2	Group 1 (15 pts): Serial glycolic acid peels (2 weeks interval) + daily topical azelaic acid (AA) 20% cream (b.i.d.) + adapalene 0.1% gel Group 2 (10 pts): Daily topical AA 20% cream (b.i.d.) + adapalene 0.1% gel Peel strength increased every other week (20%→35%→50%→70%) Study duration: 20 weeks Follow-up: 20 weeks Evaluation: MASI	25 patients Recalcitrant melasma Randomized into case (15) and control (10)	Prominent response in both groups, Results were significantly better in the group receiving chemical peels	Complex study design. Small sample size AE transient erythema and PIH in three patients of peel group.
Hurley *et al*.[61] (2002)	Randomized, investigator-blinded Split-face LOE 2	Gr A: 4% HQ cream twice daily - 8 weeks Gr B: 4% HQ twice daily + 20% GA peels every 2 weeks (20% for 4 weeks, then 30% GA for 4 weeks) Duration: 8 weeks MASI, mexameter, subjective	21 Hispanic subjects (18 were finally included) Fitzpatrick skin types IV and V enrolled Epidermal and mixed melasma	Significant reduction in both groups No significant difference between the groups	Follow-up not mentioned Small sample size

Contd...

Table 9: Contd...

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Sarkar *et al*.[62] (2002)	Open, pilot, comparative, prospective LOE 3	Group 1: 20 modified KLG formula daily + serial GP (30-40%) at 3 weeks interval for 6 sessions Group 2: 20 MKF daily Study duration: 21 weeks Evaluation: MASI, photographs, and subjective	40 Indian patients with Fitzpatrick skin types III-V with 22 women and 18 men Moderate to severe melasma epidermal type	Significant response in both groups More rapid and greater improvement in group 1	AE noted in all groups but not significant overall
Kalla *et al*.[63] (2001)	Nonrandomized, comparative study LOE 3	Gr A: 55-75% GA (68 patients) Gr B: 10-15% TCA (32 patients) Duration: continued till significant improvement Follow-up: 3 months	100 Indian patients Resistant cases were included M: F ratio 1:1.6	1. Response with TCA was more rapid 2. Relapse and hyperpigmentation was more in TCA	Duration of treatment not specified Improvement parameters not specified
Khunger *et al*.[58] (2004)	Open, pilot study, split-face LOE 4	1% tret daily versus 70% GA peel (weekly) Duration: 12 weeks Follow-up: nil Evaluation: mMASI, photograph	10 Female patients Indian	A significant decrease in both sides No significant difference between the comparing groups	Minimum side effects More tolerability with tretinoin No additional follow-up Small sample size Can be considered as a case series
Soliman *et al*.[40] (2007)	R comparative LOE 2	Gr A: 20% TCA Gr B: 20% TCA + topical 5% ascorbic acid Priming: 0.05% tret gel once daily and 4% HQ cream daily Duration: 6 weeks Follow-up: 12 weeks and 16 weeks Evaluation: MASI and patients global response	30 Female patients Epidermal melasma Skin type III and IV	13 patients (87%) in group B improved or maintained their improvement compared with only 10 patients (67%) in group A	Nonblinded
Puri[64] (2012)	Nonrandomized Comparative LOE 3	Gr A: 15% TCA Gr B: 35% GA peel (every 3 weeks) Duration: 15 weeks Follow-up: Unknown Evaluation: MASI	30 Indian patients with epidermal melasma Male: female=1:6.5	Both TCA and GP were equally effective TCA had more side effects	Randomization not specified Duration of treatment not specified Treatment protocol vague
Safoury *et al*.[65] (2009)	NR, SB, prospective Split-face MASI LOE 3	15% TCA on both sides Modified Jessner's solution on one side only (peel at 10 days interval) Duration: 10 weeks Follow-up: after 8 weeks of completion of study Evaluation: MASI	20 married females Mean age: 38.5 Skin type: III and IV	Statistically significant difference with higher improvement with combination therapy AE: significant discomfort with combined therapy side	NR, poor study design Treatment period not uniform for all the patients

Contd...

Table 9: Contd...

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Sharique *et al*.[68] (2005)	Open, uncontrolled LOE 4	Pure lactic acid (92%; pH 3.5) Duration: every 3 weeks until the desired response, max 6 sessions Follow-up: 6 months Evaluation: MASI	20 (8 dropped) Male:female=1:11 Skin type: IV	Statistically significant improvement than baseline	Poorly designed study Small sample size
Khalifa *et al*.[69] (2006)	NR, comparative Split-face LOE 3	Left face-pure lactic acid (92%, pH 3.5) versus right face-Jessner's solution every 3 weeks until the desired result Follow-up: 6 months of last session Evaluation: MASI ?	30 patients	Both showed similar and significant improvement	Poorly designed study Treatment duration not specified
Ejaz *et al*.[66] (2008)	Randomized, double-blind, prospective LOE 2 MASI	Jessner's solution every 2 weeks versus 30% salicylic acid peel every 2 weeks Daily SPF 60 sunscreen use Duration: 12 weeks Follow-up: 12 weeks Evaluation: MASI	60 subjects Skin Type IV Epidermal Melasma	Significant reduction in MASI in both the groups. But the difference was not statistically significant.	
Kodali *et al*.[67] (2010)	RCT, split-face, prospective LOE 2 Pigment reduction by narrow band reflectance spectrophotometry	Four serial peels of 20-30% salicylic acid every 2 weeks on one side of face 4% HQ on both sides Duration: 8 weeks Follow-up duration: not mentioned Evaluation: narrowband reflectance spectrophotometry	Subjects: 20 (18 completed the study) Skin type: IV	Significant reduction in pigment on both sides No significant difference found between the peeled and unpeeled sides	Comments: Good and follow-up details not mentioned

Syst Rev: Systematic review, RCT: Randomized controlled trial, R: Randomized, DB: Double blind, SB: Single blind

GA peel was compared with TCA peel in two studies. Efficacy was found to be equal[63,64] (LOE 3). However, speed of response as well as relapse was faster with TCA, indicating GA to be a better option than TCA.[63]

Overall, most studies had very small sample size and there were lack of uniformity regarding the strength of GA peel used. Only one study directly compared efficacy of GA peel with TC. The result was encouraging. Larger studies of this kind where it has been directly compared with TC or HQ are required to understand its exact efficacy.

Potency of the GA peel in comparison to HQ or TC is mostly unknown. Possibly, it has lesser efficacy. Studies are necessary in this regard. No significant long-term AE is reported. Its potency may be somewhat similar to other strong peels such as TCA peel.

Recommendation

1. *GA peel may be used in melasma (Grade A recommendation)*
2. *Its efficacy can be increased combining HQ 2% or 0.25% tretinoin. Also, it can be added to other therapies like azelaic acid or even TC to increase the overall efficacy or the speed of improvement, respectively (Grade B recommendation).*

Trichloroacetic acid peel

Evidence

Four studies evaluated efficacy of TCA (10–20%) peel. Two studies compared TCA with GA peel [Table 9]. As discussed in the section of GA peel, TCA peel was found to be of similar efficacy with different strengths of GA peel used (20–75%). Both of these drugs resulted in significant response in comparison to baseline[63,64] (LOE 3). Response with TCA peels was faster but relapse was also commoner.[63]

Addition of a topical agent, such as ascorbic acid, yields better result than in comparison with using it singly as found in a small study[40] (LOE 2).

The other study compared 15% TCA and modified Jessner's solution with 15% TCA where modified Jessner's solution proved to be useful as an adjuvant treatment with TCA in the treatment of melasma[65] (LOE 3).

Overall, the study design was poor in most of these studies. Larger and properly designed studies remained a necessity. Relapse may be high and its use requires expertise. Care must be taken to avoid AE.

Recommendation

TCA peel can be used in melasma as monotherapy, or combined with other peel like modified Jessner's solution (Grade B recommendation).

Tretinoin peel

There is still a paucity of literature on the peel formulation of the agent which has shown favorable results in a few of the recent studies. The mechanism of action of tretinoin peels is proposed to be similar to that of topical tretinoin, that is, via changes in the epidermis and dispersion of melanin.

There was no significant difference in efficacy between tretinoin 1% peel group and 70% glycolic acid in a RCT and one small study[57,58] (LOE 2, 4). However, tretinoin peel was more tolerable than GA [Table 9].

Recommendation

Tretinoin peel (1%) may be used in melasma (Grade of recommendation B).

Salicylic acid peels

Only two RCTs (80 patients) were found that evaluated efficacy of salicylic acid peel in melasma [Table 9]. One study compared the efficacy of 30% salicylic acid peel with Jessner's solution (14% salicylic acid, 14% lactic acid, 14% resorcinol in alcohol). There was no difference between these groups[66] (LOE 2).

Another group found no difference between SA peel and HQ 4%. However, the study was done in just 20 patients[67] (LOE 2).

Overall, evidence is significantly lacking. No significant AE is reported. More studies are required to understand its true efficacy and AE.

Recommendation

Salicylic acid peels may be used in melasma (Grade of recommendation B).

Lactic acid peel

Two nonrandomized studies evaluated efficacy of pure lactic acid in melasma [Table 9]. One of these was uncontrolled and another compared lactic acid peel with Jessner's peel. Both these studies reported significant improvement from baseline and no difference was observed in comparison to Jessner's solution[68,69] (LOE 4, 3).

Recommendation

Lactic acid peel may be used in melasma (Grade of recommendation B).

Jessner's peel

Two studies, one RCT and one nonrandomized trial, evaluated Jessner's solution in the treatment of melasma [Table 9].

Ejaz *et al.*[66] evaluated Jessner's solution in comparison with 30% salicylic acid where it was found that both the peels are effective in reducing melasma but the difference in efficacy was not statistically significant (LOE 2).

The other study compared 15% TCA and modified Jessner's solution with 15% TCA where modified Jessner's solution proved to be useful as an adjuvant treatment with TCA in the treatment of melasma[65] (LOE 3).

In summary, the evidence as mentioned above indicates that this peel has efficacy equal to salicylic acid peel and lactic acid peel monotherapy. However, both lactic acid (92%; pH 3.5) and salicylic acid (30%) were used in higher strength when used singly than when used in Jessner's peel. Considering the equal efficacy, Jessner's peel may be safer that the individual peel used in higher strength. However, any comment in this regard needs larger and more studies that should address both efficacy and AEs of the drugs. Overall, studies showed that Jessner's solution have yielded significant reduction in pigmentation when used alone as well as adjuvant to other peels such as TCA peel.

Recommendation

Jessner's peel may be used in melasma (Grade of recommendation B).

Overall recommendation on chemical peels

Potency of the chemical peels has never been shown to be more efficacious than standard therapies such as TC or HQ 4% in well-designed studies. In an evidence-based review by Rivas *et al.*[77] involving 40 studies and 2912 patients, it was found that GA peels are not more effective than HQ. In most of the studies, one peel has been compared with another peel. No peel has also been proven to be consistently better that other.

Different strengths of a single peel have never been compared to find the most effective yet safest strength. One Cochrane review found no difference in efficacy between Jessner's peel and salicylic acid peels both with tretinoin priming[12] (LOE 1). They also opined that meta-analysis was not possible as there was absence of homogeneity in study components. They concluded that no comment could be made on the efficacy of TCA peels, GA peels, salicylic peels or comparison between the peels.

The above-mentioned Cochrane review could not find any benefit of adding GA peel with a combination of HQ and glycolic acid cream.

Peels can have significant AE especially the strong peels such as TCA or other peels used at higher concentration. Even addition of peels such as salicylic acid peel with other agents added no additional benefit, but increased the risk of AE such as postinflammatory hyperpigmentation.[12]

Overall recommendation

1. All peels may be used in melasma (Grade of recommendation B)
2. All these peels may be used as an additional therapy to other therapy or as maintenance therapy expecting only a mild to moderate efficacy (Grade of recommendation D)
3. There is no significant advantage of one peel over another. Selection of the peel and its strength should be done based on the comfort level and experience of the treating dermatologists and the safest strength may be selected. Only experienced dermatologists should use these.

Oral tranexamic acid

Introduction

Evidence

Ten studies,[71-80] including one systematic review,[71] three RCTs, three uncontrolled studies, were found. Total patients evaluated with these studies excluding the systematic review were 1050, and almost all were of Asian origin [Table 10]. Dosage ranged from 500 to 750 mg daily, usually in divided doses. All these studies, including the review, reported the efficacy in the majority of the patients, although the degree of response was variable (LOE 1, 2, 3, 4).

Improvement was noticed as early as 4 weeks in a systematic review. Three uncontrolled studies also reported response within 4 weeks.[74-76] Some studies reported a longer median time of 2 months.[72]

None of the studies reported any significant AE except one case of deep vein thrombosis in a patient who had existing protein S deficiency.[72] Follow-up data is lacking in many of these. Maximum safe duration of treatment and minimum effective dosage are yet unknown. Relapse rates in studies varied from 7.5% to as high as 75% (in refractory melasma).[72,73]

Role of oral tranexamic acid (TXA) as adjuvant to other therapies such as TC, HQ, and laser were assessed in RCTs. One RCT evaluated addition of oral TXA on topical HQ (% unknown) and found sustained improvement at 12 weeks when TXA was added[77] (LOE 2). Three studies (2 RCTs and 1 case–control study) evaluated additional efficacy of oral TXA on Nd:YAG laser,[78] FTC,[79] and IPL.[80] All these studies reported significantly enhanced efficacy with addition of TXA to TC (LOE 2), IPL and LASER treatment (LOE 2, 4) in melasma.

Histological and immunohistochemical evaluation following oral TXA has shown decrease in epidermal pigmentation as well as melasma-associated dermal changes such as number of vessels and mast cells.[74]

Direct head-on comparison with standard therapies, such as TC and HQ, is lacking. However, such comparative studies between oral and topicals are difficult to design. Use of oral TXA has resulted in benefit among majority of the patients and addition of oral TXA with other modalities was also found to be beneficial. Importantly, most studies have been done in Asians. So far, significant AE is unknown but evaluation of coagulation profile is recommended. More studies are necessary to understand its comparative potency, relapse rates, and long-term safety.

Recommendation

Oral TXA 500–750 mg/day in a divided dose may be used in melasma expecting a mild to moderate response for a maximum period of 6 months (Grade A recommendation).

Pretreatment laboratory evaluation and monitoring during treatment is necessary.

Oral TXA can be used along with other topical therapies or IPL/Nd:YAG laser (Grade A recommendation).

Lasers

Lasers used in melasma include:

1. Pigment-specific lasers (Q-switched, long-pulsed lasers, IPL)
2. Vascular lasers (pulsed dye, Copper bromide)
3. Fractional lasers
4. Ablative lasers.

Nd:YAG laser monotherapy

Low fluence Q-switched (LFQS) Nd:YAG laser has been the most commonly evaluated laser in melasma. However, comparative efficacy of Q-switched Nd:YAG laser (532 nm) with TC or HQ is not available.

Sixteen citations were found that evaluated Nd:YAG laser in melasma and matched our initial screening specific to this topic. Two citations were excluded as they used combination drugs;[81,82] three studies were excluded as these studies actually assessed adjuvant role of oral TXA,[78] GA peel[83] and vitamin C[41] on Nd:YAG laser. Another article has been excluded because this has been retracted from PubMed.[84] Finally, 10 studies evaluated LFQS Nd:YAG laser on 446 patients[85-94] [Table 11].

Among these, six were RCTs, three were nonrandomized uncontrolled studies, and one case–control study. All the three uncontrolled studies (92 patients) reported improvement with LFQS Nd:YAG laser monotherapy (LOE 3).[85-87] Assessment was not done with standard modality in one of these.[87] Patient number was small.

Studies have documented efficacy of Nd:YAG laser as inferior to 25% TCA peel[88] and low-power fractional CO_2 laser[89] and equal to LFQS alexandrite laser (755 nm)[90] (LOE 2).

LFQS Nd:YAG laser (1064-nm) was found to result in significantly higher response when combined with IPL in comparison to IPL alone (LOE 2). However, number of patients was less and follow-up was for 2 months only.[91] Another retrospective analysis also reported similar findings[94] (LOE 4).

Table 10: Evidence on oral tranexamic acid

Authors	Type of study and LOE	Study modality	Patient profile	Results	Comments/weakness
Tse *et al*.[71] (2013)	Systematic review LOE 1	Review of randomized controlled trials as well as nonrandomized trials and *in vitro* studies	Caucasian and African	Effective dose-250 mg 2-3 times daily	
Karn *et al*.[77] (2012)	RCT LOE 2	Oral TXA 250 mg BD + HQ (% unknown) versus HQ (% unknown) Duration: 3 months Follow up: nil Evaluation: MASI	260 Nepalese patients (130 in each group)	Both group significant response (8 wks) TXA group sustained response (12 wks) Better response to TXA in epidermal melasma	
Padhi *et al*.[79] (2015)	RCT LOE 2	Oral TXA (250 mg BD) + FTC versus FTC Duration: 8 weeks Follow up period: 6 mo Evaluation: MASI	40 Indian patients	Faster, higher (statistically significant) response at 4 weeks and 8 weeks and persistent response at 6 mo with combination therapy	1. Small sample size 2. No mention of MASI at 6 months 3. Pseudo-randomized study 4. No blinding of observer
Shin *et al*.[78] (2012)	RCT LOE 2	Oral TXA 250 mg TDS, combined with Nd: YAG laser versus LASER alone Duration: 8 weeks Follow-up: nil Evaluation: mMASI and clinical improvement	48 Korean female patients (44 completed)	Significantly higher reduction in mMASI at 4 weeks after second laser treatment in combination group	Sample size: small Oral medication used contained ascorbic acid and L-cysteine in addition to TXA Short follow-up Pharmacy supported trial
Na *et al*.[74] (2013)	Open, uncontrolled, NR LOE 3	Clinico-histopathological analysis, oral TXA 250 mg TDS Duration: 8 weeks Follow up: nil Evaluation: mexameter; histopathology (Fontana-Masson Stain), IHC (CD31 Ab, anti-tryptase Ab)	25 Korean female patients	Improvement in melanin index: statistically significant Improvement in erythema index: statistically insignificant Effective as early as 4 weeks	Small sample size TXA Tablets contained other components such as L-cysteine, ascorbic acid Topical TXA was also used Pharma sponsored study
Wu *et al*.[74] (2012)	O, uncontrolled, NR LOE 3	Oral TXA 250 mg BD Duration: 6 months Follow up for 6 months Evaluation: physicians' assessment and self-assessment	74 Chinese female patients	Improvement seen at end of 4 weeks, 8 weeks, and 6 months: 82.4%, 94.6%, and 95.9% patients, respectively 6-month follow-up: recurrence in 9.5% patients Gastrointestinal side effects in 5.4%, hypomenorrhea in 8.1% Rarely dizziness, alopecia, drowsiness, and hyposexuality	Degree of improvement not assessed Subjective mode of assessment No control group This article specifically mentions nonresponsiveness
Li *et al*.[75] (2014)	Open label, uncontrolled, nonrandomized LOE 3	Oral TXA 250 mg TDS Duration: 16 weeks Follow up: nil Evaluation by skin color scale and physician' assessment	35 Chinese patients (32 completed) 33 females and 2 males Mild or moderate melasma	Significant improvement at 4, 8, 12, and 16 weeks Gastrointestinal side effects in 12.5% patients Menstrual side effects in 2 patients Drowsiness in one patient	Assessment methods not standard

Contd...

Table 10: Contd...

Authors	Type of study and LOE	Study modality	Patient profile	Results	Comments/weakness
Cho *et al*.[80] (2013)	RS, case-control LOE 4	Oral TXA 500 mg/day with IPL/Nd: YAG laser versus IPL/Nd: YAG LASER Duration: 6 months Follow up: nil Evaluation: mMASI	51 Korean female patients	Significantly better improvement in TXA group (43.8% versus 23.6%)	Retrospective study
Lee *et al*.[72] (2016)	RS LOE 4	Oral TXA Duration: 4 months	561 Asian patients	89.7% of patients had improvement Response within 2 months Relapse rate of 27.2% One case of deep vein thrombosis due to underlying protein S deficiency	Retrospective study
Tan *et al*.[73]	RS LOE 4	Oral TXA 250 mg BD Topical agents were also used Duration: 2-8 months Evaluation: MASI and physicians global assessment	Mixed race study of 25 patients 23 Females and 2 males Melasma refractory to topical agents	Mean MASI improvement: 69% at 3 months 72% had relapse of melasma within 2 months of stopping TXA despite continuance of topical agents	Retrospective study. Small sample size indicates effectiveness of TXA in refractory melasma High relapse rate

Table 11: Evidence on lasers in melasma

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/weakness
Alsaad *et al*.[83] (2014)	Split-face RCT LOE 2	5 ns QS Nd: YAG versus 50 ns QS Nd: YAG laser Fluence 1.6 J/cm^2, 5-6 mm spot size, 2 passes Duration: 3 sessions 1 month apart Follow-up: 6 mo Evaluation: MASI, spectrophotometer	10 patients Saudi Arabia	No significant difference in improvement 50 ns side had lesser pain	Patient number less Laser treatment sessions relatively less Multiple modalities (microdermabrasion and topicals) were used along with lasers
Moubasher *et al*.[88] (2014)	RCT LOE 2	QS Nd: YAG laser versus TCA peel Group A: TCA 20% epidermal Group B: TCA 25% epidermal, dermal and mixed Group C: TCA 30% dermal and mixed Group D: QS-Nd: YAG 532 nm 0.8 J/cm^2, 4-6 mm spot size for epidermal and 1064 nm 3-3.8 J/cm^2, 4-6 mm for dermal melasma Duration: TCA peel every 2 weeks up to 8 sessions and laser every month up to 6 sessions Follow-up: 3 mo Evaluation: MASI	65 patients Egypt	TCA group B showed significantly greater reduction in MASI (64.7%) Q-switched Nd: YAG 532 nm showed higher incidence of postinflammatory hyperpigmentation	Method of randomization not mentioned in the study

Contd...

Table 11: Contd...

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/weakness
Yun *et al*.[91] (2015)	Double-blinded RCT LOE 2	LFQS Nd: YAG laser (1064-nm) and IPL versus IPL only Nd: YAG-fluence 1.5-2 J/cm2, 6 mm spot size, 4-6 passes IPL-F: 13-15 J/cm^2, 2 passes Duration: 6 sessions at 2 weeks interval Follow-up: 2 mo Evaluation: MASI	24 patients Korea	Combination group showed significantly greater decrease in partial MASI	Patient number relatively less Cases were followed up for only 2 months after last session
Vachiramon *et al*.[92] (2015)	Split-face RCT LOE 2	LF SQ Nd: YAG 1064-nm laser and IPL versus IPL monotherapy Nd: YAG: 2.6-2.8 J/cm^2, 6 mm spot size, 3 passes, weekly, both sides IPL (555-950 nm filter) 6.8-8 J/cm^2, double pulse, pulse duration 2.5-3 ms. Biweekly, one half of face Duration: 5 sessions at 1-week intervals Follow-up: 3 months Evaluation: mMASI	18 patients Thailand	Combined treatment side showed faster improvement Recurrence of melasma was higher in the combined side One patient developed guttate hypomelanosis on both sides	Patient number less Higher recurrence rates with combined
Fabi *et al*.[90] (2014)	Split-face double-blinded RCT LOE 2	LFQS Nd: YAG laser versus LFQS alexandrite laser (755 nm) Nd: YAG: Fluence 1-2 J/cm^2, 8 mm spot size, 1-8 passes Alexandrite-fluence 1.2 J/cm^2, 8 mm spot size, 1-2 passes Duration: 6 sessions weekly Follow-up: 6 months Evaluation: mMASI	20 patients California	Improvement in mMASI was more with QS Nd: YAG (27% versus 19%) but statistically insignificant	Patient number less Alexandrite laser though readily absorbed by melanin compared to QS Nd: YAG, did not have any significant adverse effects
Jalaly *et al*.[89] (2014)	Split-face double-blind RCT LOE 2	Low-power $FrCO_2$ laser versus LFQS 1064 nm Nd: YAG laser LFQS: 1.5-2J/cm^2, 7 mm, 5 passes Fr CO2: 1 W power, density 0.7 Duration: 5 sessions every 3 weeks Follow-up: 2 months Evaluation: mMASI	40 patients Tehran	Significantly higher decrease in melanin index in $FrCO_2$ side (15.09 ± 13.39 versus 5.97 ± 7.66) and mMASI (8.15 ± 6.53 versus 2.3 ± 3.73)	Shorter follow-up duration The time interval between two sessions of QS Nd: YAG laser was more compared to similar studies using laser toning
Kim *et al*.[85] (2016)	Nonrandomized LOE 3	Photoacoustic twin pulse mode of LFQS Nd: YAG laser 1064 nm Fluence 2.5 J/cm^2, 7 mm spot size, 5-7 passes Duration: 5 sessions at 2 weeks interval Follow-up: 2 weeks Evaluation: MASI, chromameter	22 females Korean	Significant improvement	Patient number relatively less Short follow-up

Contd...

Table 11: Contd...

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/weakness
Hofbauer Parra *et al.*[86] (2016)	Nonrandomized LOE 3	LFQS Nd: YAG Fluence 0.8-1.6 J/cm^2, 8 mm spot size, 1-3 passes Duration: 10 sessions at weekly interval Follow-up: 6 mo Evaluation: mMASI, histopathology	20 patients Brazil	Reduction of mMASI scores was by 21-75% Recurrence in 81% at 6 months follow-up	Patient number relatively less High recurrence rate
Sim *et al.*[87] (2014)	Nonrandomized LOE 3	LFQS 1064 nm Nd: YAG laser Fluence 2.8 J/cm2, 8 mm spot size Duration: 15 sessions at 1 week interval Follow up: nil Evaluation: patient and investigators global evaluation Janus imaging system	50 Females Korea	Global response-good improvement Janus imaging system showed significant improvement	Assessment with MASI was not used as a parameter to assess improvement Follow-up of achieved improvement was not performed
Choi *et al.*[94] (2015)	Retrospective analysis LOE 4	Dual toning-LFQS and long-pulse Nd: YAG versus LFQS Nd: YAG laser Monotherapy: QS Nd: YAG: 2.5-3.0 J/cm2, 6 mm spot size Dual toning: QS Nd: YAG: 2.1-2.5 J/cm^2, 6 mm spot size followed by LP Nd: YAG: 15-17 J/cm^2, 7 mm spot size Duration: 10 sessions weekly Follow-up: 6 months Evaluation: mMASI	177 patients in monotherapy and 183 patients in dual-mode therapy Korea	Combined therapy group showed higher decrease in mMASI (3.6 versus 3.0) and significantly lower adverse effects such as mottled hypopigmentation and rebound hyperpigmentation (14.1% versus 1.1%)	Short follow-up duration

Various parameters of LFQS Nd:YAG laser have been tried to find out the best one. No significant difference was found between the pulse duration of 5 and 50 ns[93] (LOE 2). Combination of LFQS and long-pulse Nd:YAG resulted in higher decrease in mMASI (3.6 versus 3.0) and significantly lower AEs such as mottled hypopigmentation and rebound hyperpigmentation in comparison to LFQS Nd:YAG laser[94] (LOE 4).

Overall, most of the studies had methodological limitations. Sample size was small and follow-up was limited. Randomized, blinded comparative study with standard drugs such as TC or HQ could be of help to assess its real efficacy.

Recommendation

LFQS Nd:YAG laser (1064 nm) monotherapy is not recommended in melasma.

Nd:YAG laser combination therapy

Efficacy of LFQS Nd:YAG laser was found to be increased when adjuvants such as oral TXA (48 patients, LOE 2),[78] GA peel[83] (15 patients, LOE 2), and vitamin C[41] (8 patients, LOE 3) were added. All such combinations were better than the laser monotherapy. Thus, it may be prudent to use such combination instead of laser monotherapy (Grade D recommendation). However, small number of patients has limited these results to be translated into recommendation. More studies are necessary. See other sections for more details.

Alexandrite laser

Alexandrite laser, though being more pigment-specific compared to Q switched Nd:YAG laser, is expected to have lesser postinflammatory hyperpigmentation. Statistically insignificant, yet higher efficacy of LFQS Nd:YAG laser in comparison to LFQS alexandrite laser (755 nm) was reported in a study by Fabi *et al*. in a very small split-face double-blinded RCT among 20 patients[90] (LOE 2).

Recommendation

Not recommended until further evidence is available.

Q-switched ruby laser

No single study was found that evaluated QSRL monotherapy in melasma. Only one uncontrolled study

evaluated 694-nm fractional Q-switched ruby laser (fluence 2.5–3.5 J/cm^2, 7.1 × 7.1 mm spot size, 27.7% area coverage) combined with sonophoresis on levorotatory vitamin C.[81] After four sessions at 2 weeks interval, MASI score decreased by 35% from baseline at follow-up of 3 months after last session.

Recommendation

Not recommended until further evidence is available.

Ablative lasers

Fractional and ablative lasers as single therapies are no longer used due to higher incidence of postinflammatory hyperpigmentation. These have been used with lower fluences.

Fractional CO_2 laser

In a split-face double-blinded RCT among 40 patients, low-power fractional CO_2 laser was compared to low-fluence Q-switch 1064 nm Nd:YAG laser.[89] Fractional CO_2 resulted in significantly higher decrease in melanin index in fractional CO_2 side (15.09 ± 13.39 versus 5.97 ± 7.66) and mMASI (8.15 ± 6.53 versus 2.3 ± 3.73) (LOE 2). However, there are many issues in considering this study in recommending this laser in Indian population. Apart from the cost, low-power fractional CO_2 laser is an ablative laser. The study was done in non-Asian population. Patient population was only 40. Follow-up was short.

Recommendation

Not recommended in melasma.

Er:YAG laser

Only one study (uncontrolled) on Er:YAG laser (fluence 1 J/cm^2, 5 mm spot size, 2 passes) reported significant improvement in MASI among 15 patients.[95] However, postinflammatory hyperpigmentation was universal (LOE 3).

Recommendation

Not recommended.

Er:Glass laser 107

Only one nonrandomized follow-up study was found that reported marked improvement of more than 75% decrease in MASI in 67.1% patients after 1 month of therapy.[82] However, on follow-up, this became 21.1% at 6 months follow-up.

Recommendation

Not recommended.

Vascular laser

These lasers have an indirect effect in melasma by targeting epidermal vascular endothelial growth factor and dermal vasculature and are more useful in angiogenic melasma.

Copper bromide laser

One nonrandomized study on copper bromide laser (dual-wavelength 511 and 578 nm, fluence 7–19 J/cm^2, 1 mm spot size, 2 passes) could not find any significant improvement among 24 patients in Thailand.[95]

In a split-face RCT among just 20 patients, copper bromide laser was not found superior to TC.[21]

Recommendation

Not recommended until further evidence is available.

Photoprotection in melasma

Evidence

There has been no study among Asians. Four studies were found and all were done among Caucasians. Three out of these four were RCT. Total patients evaluated were 339. Effect was assessed with MASI or calorimetrically [Table 12].

Role of broadband sunscreen was found to be beneficial in melasma management[97,98] (LOE 2, LOE 4). Broad spectrum sunscreen along with protection against visible light was found to be better than when visible light was not guarded[99,100] (LOE 2).

Recommendation

Broad spectrum sunscreen along with visible light protection is recommended in any melasma management strategy (Grade A recommendation).

Miscellaneous drugs

Lignin peroxidase

Only three publications (1 RCT and 2 uncontrolled studies) were found among 142 subjects. All these three studies were done using the product from a single company. More studies among larger number of subjects are necessary to recommend this drug [Table 13].

One RCT on 51 Asian patients compared LP with HQ 2% or placebo in a split-face style that reported significantly higher efficacy than HQ 2%. Improvement was seen as early as 7 days[101] (LOE 2). However, it was a very short duration study (31 days).

One nonrandomized study among 60 subjects reported equal efficacy with HQ 4% and higher efficacy than placebo.[102] LP was, however, reported to be superior in improving skin texture and roughness as compared to 4% HQ[102] (LOE 3).

Another uncontrolled open label study also reported significant benefit in melasma[103] (LOE 3). More studies are necessary to assess the efficacy, long-term AE, and relapse rate.

Recommendation

Lignin peroxidase is recommended in melasma (Grade B recommendation).

Table 12: Evidence on sun protection

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Boukari *et al*.[99] (2015)	RCT LOE 2	Sunscreen protecting against UVA, UVB, and visible light versus UVA/UVB without visible light Duration: 6 mo Follow up: Unknown Evaluative: MASI	40 Caucasians patients Male: female = Unknown	Protection against broad spectrum sun protection including VL better	Small sample size
Vazquez *et al*.[98] (1983)	Double-blind RCT LOE 2	Efficacy of a broad-spectrum sunscreen versus placebo Duration: Unknown Follow-up: Unknown Evaluation: Unknown	53 Caucasians Male: female = Unknown	Positive role of broad spectrum sun protection	
Castenedo-Cazares *et al*.[100] (2014)	Double-blind RCT LOE 2	Broad spectrum UV protection along with iron oxide (for VL) versus regular UV broad spectrum sunscreen Duration: 8 weeks Evaluation: MASI, colorimetry and histology	61 Caucasians (Mexico) Male: fem = Unknown	Broad spectrum UV protection sunscreen with iron oxide is better	Small sample size Short duration
Lakhdar *et al*.[97] (2007)	Case series, uncontrolled study LOE 4	Broad-spectrum sunscreen Duration: 12 mo Follow-up: nil Evaluation: colorimetry	185 Caucasians Male: fem = Unknown	Effective	

Table 13: Evidence on lignin peroxidase

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/weakness
Mauricio *et al*.[101] (2011)	Double-blind, placebo-controlled, split-face, RCT LOE 2	LP cream versus 2% HQ or placebo on either side of face Duration: 31 days Evaluation: mexameter	51 Female Asian patients	LP cream provided significant skin-lightening as compared to HQ Rapid effect, seen as early as 7 days	Follow-up: not known It was a product named Melanozyme by Syneron, Yokneam Illit, Israel)
Draelos *et al*.[102] (2015)	Split-face, nonrandomized prospective study LOE 3	Two cohorts- LP versus placebo and LP versus 4% HQ Duration: 12 weeks Follow-up: nil Evaluation: MASI, dermospectrophotometer	60 British women (18-65 years) Facial dyspigmentation including melasma	LP superior to placebo but equal to HQ 4%.	Follow up - nil
Zhong SM *et al*.,[103] 2015	Uncontrolled open label study LOE 3	Effect of LP on melsama Duration-8 weeks Follow up- 14 weeks Evaluation MASI, spectrophotometer	31 women, Chinese	LP significantly reduced melasma pigmentation	Additional benefit of increased luminance of facial skin Uncontrolled study Product provided by Syneron Medical Inc)

N-acetyl glucosamine

In the only available study, which is a randomized, double-blinded, split-face study done in 30 females (aged 20–50 years) and compared cream A (4% NAG and 2% nicotinamide) and cream B (4% HQ) for 12 weeks, efficacy of NAG and nicotinamide was found to be slightly more and

the side efforts were slightly less than HQ group. However, the difference in mMASI was not statistically significant at the end of the study[104] (LOE 2). The limitations of that study were small sample size, short duration trial, and the absence of NAG monotherapy [Table 14].

Recommendation

NAG cannot be recommended due to lack of evidence.

Linoleic acid

In a 6-week, double-blind, RCT among 60 patients, linoleic acid (LA) in combination with lincomycin and betamethasone valerate was found to result in higher improvement than a combination of the latter two or vehicle[105] (LOE 2). Addition of LA did not produce any significant AE [Table 14].

Table 14: Evidence on evidence on NAG, LA, silymarin, pidobenzone, and methimazole

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Iraji *et al*.[104] (2009)	RCT, double-blind, split-face LOE 2	Combination of 4% NAG and 2% nicotinamide versus 4% HQ Duration: 12 weeks Evaluation: Unknown	30 females (aged 20-50 years)	Efficacy of NAG + nicotinamide slightly more than HQ (insignificant) NAG + nicotinamide slightly safer than HQ	Limited sample size Follow-up: not known
Mu-Hyoung Lee *et al*.[105] (2002)	Double-blind, RCT LOE 2	Comparison between the following: Gr A: Vehicle Gr B: 2% Lincomycin + 0.05% Betamethasone valerate Gr C: 2% Lincomycin + 0.05% Betamethasone valerate + 2% Linoleic acid Sunscreen added Duration: 6 weeks Follow-up: nil Evaluation: MASI	47 Korean female (age range, 28-54) years Fifteen women in Gr A, sixteen women each in gr B and C	Combination of Gr C was significantly better than other groups	Short duration trial BV may cause depigmentation on own Follow-up: not known
Elfar *et al*.[106] (2015)	Nonrandomized, comparative study, LOE 3	Comparison between Gr A: TXA injection (4 mg/ml) every 2 weeks, Gr B: silymarin cream (14 mg/ml) twice daily, Gr C: 50% GA peels Duration: 12 weeks Follow-up: 12 weeks Evaluation method: MASI	60 Egyptian female patients, 20 patients in each group	Topical silymarin showed moderate benefit in melasma, parity with GA peel, superior to intradermal TXA	Follow-up: not known
Zanieri *et al*.[107] (2008)	Case series, LOE 4	4% pidobenzone gel Duration: 16 weeks Follow-up: 3 mo Evaluation: MASI	20 female (aged 20-46 years) Fitzpatrick phototype II to VI	2 patients complete clearing, 6 patients significant reduction, 6 patients mild response	
Malek *et al*.[108] (2013)	Case report, LOE 4	5% Methimazole Duration: 8 weeks Follow-up: nil Evaluation method: clinical evaluation	Two HQ-resistant melasma patients, 50-year-old Hispanic woman and 34-year-old Middle Eastern woman	Significant improvement of melasma	Theoretical risk of systemic thyroid adverse effects of methimazole

Recommendation

There is not enough evidence to recommend use of linoleic acid in melasma.

Silymarin

Only one study was found to evaluate the efficacy of topical silymarin among 60 females[106] [Table 14]. It was compared with intradermal TXA injection and 50% GA peeling. Topical silymarin showed only moderate benefit in melasma with efficacy insignificantly less than GA peel but superior to intradermal TXA (LOE 3).

Recommendation

There is not enough evidence to recommend the use of topical silymarin in melasma.

Pidobenzone

The treatment with pidobenzone 4% (K5 lipogel) twice per day for 16 weeks caused significant reduction in MASI scores by at least 50% in as many as 70% patients without any major AE[107] (LOE 4) [Table 14].

Recommendation

There is not enough evidence to recommend use of pidobenzone cream in melasma.

Methimazole 5%

In two HQ-resistant melasma patients, application of 5% methimazole cream once daily resulted in significant improvement of melasma in both patients after 8 weeks and was well tolerated[108] (LOE 4) [Table 14].

There is a theoretical risk of systemic AE of methimazole. A single study did not show any AE on thyroid but more studies are required to confirm this.[109]

Recommendation

There is not enough evidence to recommend the use of methimazole cream in melasma.

Rucinol

Three double-blind vehicle controlled small RCTs (including one that used liposomal rucinol) evaluated rucinol (0.1–0.3%) in total 75 patients with melasma. All the studies found significantly better response than vehicle[110-112] (LOE 2). Follow-up was absent and information on relapse was unavailable. None of the study compared this with standard drugs such as HQ. Moderate-to-severe AE was also reported[110] [Table 15]. One uncontrolled open cohort among 52 Indian patients also reported moderate efficacy[113] (LOE 3).

Recommendation

Rucinol is not recommended in melasma till further evidence suggests advantage over AE.

4-Hydroxyanisol (mequinol)

There are many studies on its beneficial role in solar lentigines.[114-118] However, only one study is available on melasma and this is a case series on 5 male patients (3 Hispanic and 2 white)[131] [Table 16].

Mequinol 2% was used along with tretinoin 0.01% topical solution. Four of 5 patients achieved complete clearance of melasma at 12 weeks, and 1 patient showed moderate improvement[119] (LOE 4).

Side effects were minimal. There was an uncontrolled study without any proper evaluation method. Moreover, mequinol was used along with tretinoin. However, all patients were initially resistant to HQ.

Recommendation

There is not enough evidence to recommend the use of topical mequinol in melasma.

Niacinamide

Four RCTs were found that assessed niacinamide.[26,120-122] However, two studies included patients with different causes of facial hyperpigmentation in addition to melasma[121,122] and another one evaluated a combination cream with niacinamide as one ingredient.[1] Thus, only one double-blind RCT evaluated efficacy of niacinamide monotherapy in melasma, and it compared the efficacy with 4% HQ [Table 16].

This study, done among only 27 females, showed good to excellent reduction in pigmentation in 44% of nicotinamide-treated areas compared to 55% with 4% HQ[26] (LOE 2). Side effects of erythema, pruritus, and burning were less frequent and milder with nicotinamide compared to hydroquinone (18% versus 29%). However, there was no follow-up.

Thus, currently, there is significant lack of evidence. More and larger studies are needed.

Recommendation

Niacinamide can be used in melasma (Grade B recommendation).

Triamcinolone injection

One RCT among 42 patients found sub-epidermal triamcinolone injection to be superior to Kligman's formula in improving melasma but AE such as telangiectasia and atrophy were observed[123] (LOE 2).

Recommendation

Not recommended.

Topical betamethasone 17-valerate

No publication was found within the period searched (year 2000 onwards).

Table 15: Evidence on rucinol

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Huh *et al*.[111] (2010)	Double-blind, vehicle-controlled and split-face RCT LOE: 2	0.1% Liposome-encapsulated rucinol versus vehicle Broad spectrum sunscreen used Duration: 8 weeks Follow-up: nil Evaluation: mexameter	23 Korean female patients	Significant improvement after rucinol	Small sample size Short duration trial Follow-up: nil
Huh *et al*.[112] (2010)	Double-blind, vehicle-controlled, split-face comparative study LOE 2	4-N-butylresorcinol 0.1% cream versus vehicle Applied twice daily on either side of face Broad spectrum sunscreen used Duration: 8 weeks Follow-up: nil Evaluation: mexameter	20 Korean female (age range: 28~49 years) Fitzpatrick III-V	Statistically significant improvement Mild erythema and itching were seen in 2 patients	Small sample size No follow-up AE noted
Khemis *et al*.[110] (2007)	Double-blind split-face RCT LOE 2	0.3% Rucinol versus vehicle 1st Phase - 12 weeks, split-face application (drug and placebo) 2nd Phase: 12 Full-face application of rucinol Duration: 24 weeks Follow-up: 12 weeks Evaluation: Chromametry	32 females (18 Europeans, 13 Arabians, and 1 Indian) Fitzpatrick II-IV	Statistically significant reduction with rucinol AE noted in 12 patients. Mild to moderate AE such as stinging, burning or pruritus, erythema and 1 severe required blepharoplasty	Study design complex and evaluation method: not standard AE of the drug is important
Madan Mohon *et al*.[113] (2016)	Open-label, uncontrolled trial LOE 4	4-n-Butylresorcinol 0.3% cream Duration: 8 weeks Follow-up: nil Evaluation: MASI	52 Indian patients (47 females and 5 males) Mal	Statistically significant reduction of pigmentation in treated patients	Indian study

Table 16: Evidence on mequinol and niacinamide

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Keeling *et al*.[119] (2008)	Case series LOE 4	Mequinol 2% and tretinoin 0.01% Duration: 12 weeks Follow-up: up to 16 weeks	5 American men	Complete clearance of melasma at 12 weeks in 4 patients. Results maintained at the 16th week	Individual benefit of mequinol not assessed
Navarrete-Solís *et al*.[26]	DB, SF, RCT, LOE 2	Topical niacinamide versus HQ Duration: 8 weeks Follow-up: nil Evaluation: Unknown	27 Mexican female patients Fitzpatrick skin type IV and V	All patients showed pigment improvement with both treatments (statistically insignificant) HQ was better in reducing mast cell infiltrate improvement of solar elastosis	Follow-up: nil

Clobetasol propionate

In an uncontrolled study, 10 patients of melasma were treated with topical clobetasol propionate (0.05%) for 8 weeks. After 6–8 weeks 80–90% clearance of pigmentation was observed in 7 patients[125] (LOE 3). However, pigmentation reappeared 2–3 weeks after stopping treatment, even reaching pretreatment state during the next 4–6 months of follow-up. Three patients had to stop therapy after 4 weeks because of local atrophy and striae.[47]

In another single-blind pilot study, split-face comparison study among 30 Indian patients with melasma, initial 8 weeks of 0.05% clobetasol propionate cream followed by 20% azelaic acid cream for the next 16 weeks resulted in higher improvement than azelaic acid monotherapy[125] (LOE 2).

Recommendation

Not recommended.

N-acetyl-4-S-cysteaminylphenol

In a retrospective case series of 12 patients of melasma, 4% *N*-acetyl-4-S-cysteaminylphenol was applied twice daily for up to 6 months. There was marked improvement in 8 patients, moderate improvement in 3 patients, and almost complete clearance of melasma in 1 patient. Acneiform eruptions were noted in 1 patient[126] (LOE 4).

However, there were many weakness of the study protocol. Apart from the small sample size, no standard evaluation criteria were used; biopsy was done in 2 patients; control was there in just 3 patients; and follow-up duration was variable.

Recommendation

There is not enough evidence to recommend the use of topical N-acetyl cysteaminylphenol in melasma.

Magnolignan

A single, uncontrolled study evaluated a specific product containing 0.5% Magnolignan® on 51 female patients with facial pigmentation (not exclusively melasma after 6 months, authors reported improvement)[127] (LOE 3). However, evaluation method was not standard [Table 17].

Recommendation

There is not enough evidence to recommend the use of topical Magnolignan in melasma.

Orchid extracts

Only single study was found and it was an open, split-face 8-week trial. Plant extracts (orchid extracts) were compared with vitamin C among 48 Japanese female adult volunteers (30–60 years) with melasma and/or lentigosenilis. The extract was found to be efficacious clinically, in colorimetric measurements and subjectively using a questionnaire[128] (LOE 3) [Table 17].

The extract contained various components, evaluation method was not standard, and comparison was done with vitamin C, which in itself is a weak depigmenting agent.

Recommendation

There is not enough evidence to recommend the use of topical orchid extract in melasma.

Dioic acid

In the only available study done among 96 Mexican females, 1% dioic acid cream was found to improve melasma significantly (MASI) and similar in efficacy to that of 2% HQ cream[129] (LOE 3) [Table 17].

Recommendation

There is not enough evidence to recommend the use of topical dioic acid in melasma.

Octadienedioic acid

No study in melasma available. One Chinese study compared 1% ODA cream with 2% arbutin in forearm for 8 weeks to evaluate its ability to reduce melanin index.[130]

Recommendation

Not possible.

B-carotene

Only single-cohort study done long back is available. Among the 31 Indian patients (26 females and 5 males), clinical improvement was noticed in all except 2 at 8 weeks. Nine patients who continued the drug had further improvement of lower grade[131] (LOE 3). No major AE reported [Table 18].

Recommendation

There is not enough evidence to recommend the use of topical beta-carotene in melasma.

Licorice

No study on licorice monotherapy available. A single RCT among 56 female subjects (89% concluded the study) compared the efficacy of a combination of emblica, licorice, and belides 7% with 2% HQ. Both the group had similar efficacy[132] (LOE 2) [Table 18].

There were many weaknesses of the study. It was a complex combination of licorice; there was no follow-up and evaluation method was poorly defined. Mild burning sensation is reported.

Recommendation

There is not enough evidence to recommend the use of topical licorice in melasma.

Table 17: Evidence on Magnolignan, orchid extract, and dioic acid

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Takeda *et al*.[127] (2006)	Uncontrolled prospective study, LOE 3	0.5% Magnolignan® topical Duration: 6 mo Follow-up: nil Evaluation: MASI	51 Female patients with melasma and other indications such as senile lentigo Origin: Oriental	Statistically significant improvement of melasma	Lightening of nonpigmented healthy skin also seen Follow-up: not known
Tadokoro *et al*.[128] (2010)	Open, split-face study, LOE 3	Plant extracts including orchid extracts versus 3% vitamin C derivative Duration: 8 weeks Follow-up: not known Evaluation: colorimetry	48 Japanese females (30-60 years) Melasma and/or lentigo senilis	Statistically significant improvement with plant extract, parity with vitamin C	Comparison done with vitamin C, a weak depigmenting agent Short duration trial
Tirado-Sanchez *et al*.[129] (2009)	Open, nonrandomized comparative study, LOE 3	1% Dioic acid versus 2% HQ Duration: 12 weeks Follow-up: nil Evaluation method: MASI	96 Mexican female patients	Significant reduction in MASI, parity with HQ, lesser side effects than HQ	Follow-up: not known

Table 18: Evidence on B-carotene and licorice

Author name with year	Type of study and level of evidence	Study modality	Patient profile	Results	Comments/ weakness
Kar *et al*.[131] (2002)	Case-control study, LOE 3	B-carotene lotion versus base sunscreen added Duration: 8-24 weeks Follow-up: nil Evaluation: melasma intensity (MPI) index	43 Indian patients study group, 31 Indian patients (F:M=26:5) 12 control group (10:2)	Significant benefit among 29 patients after 8 weeks	Short duration trial Follow-up: not known Evaluation method not standard
Costa *et al*.[132] (2010)	RCT, Phase IV study	Proprietary formulation containing emblica, licorice and belides 7% (twice daily) versus 2% HQ (once daily) Broad spectrum sunscreen used Duration: 60 days, Follow-up: nil Evaluation: Photography (Visia)	56 females (18-60 years), 89% concluded Phototype I to IV	Significant reduction in pigmentation with both formulations No difference between them. AE such as burning and acneiform eruption noted but overall, lesser than those with HQ	No standard evaluation criteria used No follow-up Proprietary combination product

Other drugs

There were some reports of improvement in pigmentation but no human clinical studies in melasma were found for the following molecules/drugs:

Aloesin, ebselen,[133] cinnamic acid,[134,135] pyronic acrylic acid inhibitors,[136] zinc dihydrolipoylhistidinate,[137] resveratrol, 8-methoxycinnamaldehyde, soy, flavonoids, and alpha tocopherol ferulate.

Recommendation

There is not enough evidence to recommend the use of any of these drugs in melasma.

Suggested therapeutic recommendation for melasma

Before a step-ladder treatment protocol is suggested, it may be prudent to classify the available melasma drugs. The classification has been done based on the potency, safety, and the type of therapy. Evidence (whenever available, see the earlier section) and opinion of the team members have been utilized to prepare this classification.

Classification of melasma drugs

1. Class 1: Daily TC*. Maximum allowable duration for daily therapy is 12 weeks
2. Class 2: HQ 4% (Maximum allowable duration for daily therapy 3 months), azelaic acid 20% cream (Maximum allowable duration for daily therapy 6 months)
3. Class 3: HQ 2%, KA 2%, topical retinoids, chemical peels, and various other drugs with known efficacy (see the previous text). Most of these drugs are safer

and less potent than the first and second line. It is considered to be safer than those without any strong evidence in this regard. Although most of the studies have recommended the use for 3 months, maximum allowable duration may be longer. However, no definite information is available at least for some of these

4. Class 4: Oral TXA (500–750 mg/day) for a maximum period of 6 months
5. Class 5: Laser. LFQS Nd:YAG laser is most preferred Most studies have used up to 6 sessions and some up to 15 sessions.

Outside any category: Sunscreen6.

*TC, unless specifically mentioned, usually means fluocinolone acetonide-based TC (FTC).

Step-wise treatment protocol for melasma

Flowcharts [Figures 1 and 2] have been presented for understanding step-wise management protocol of melasma. It must be understood that there may be various situations outside the purview of this protocol. Entire previous sections will help the physician to take right decision in any such special situation.

Some rules for using the flow chart

1. In the flowchart, change from one drug to another should ideally be done when it reaches the maximum allowable period (if available) for that particular drug or earlier if there is an AE
2. Sunscreen should be used in all cases
3. TC indicates fluocinolone-based TC
4. Combination treatment indicates all possible combinations with drugs that can be used. Treating physician should select various combinations according to the evidence cited in earlier section and use his/her clinical knowledge
5. One drug may not be used when there is known information of poor response in the recent past, presence of signs of AE that might be due to same/similar drug or might be aggravated by this drug, and when the maximum allowable limit for a continuous therapy has crossed
6. The starting point of treatment for a particular patient in the step ladder has to be judged by the physician
7. Drug holiday, even for many months, after most of the options have been exhausted is a logical step before reinitiating of the treatment.

Conclusion

A therapeutic guideline for melasma that will be universally acceptable is difficult to design even when it is evidence based. Generally, a step-ladder therapeutic protocol follows a principle where efficacy is the primary criteria for selecting a drug over other. However, practically, efficacy may not be the priority in many cases of melasma. Due to the availability of almost all topical formulations over-the-counter in India, it is not uncommon to find patient who has already applied TC, HQ, and other topical steroid formulations, even much beyond the safety limit prior to seeking opinion of a dermatologist. These patients usually have obvious manifestations of AE related to these drugs and are unsuitable for any further exposure to similar drugs. Thus, safety becomes the priority in these situations.

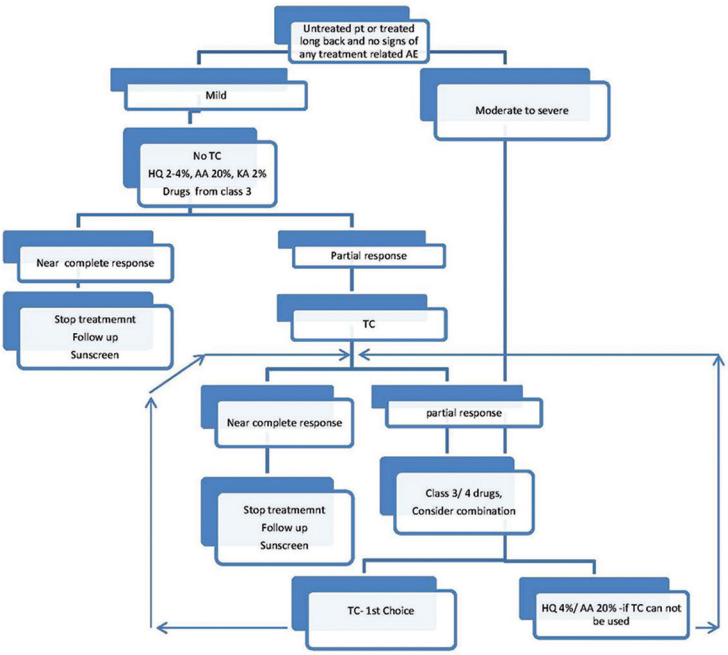

Figure 1: Step-wise management plan for "new patients" or "patients who were treated long back"

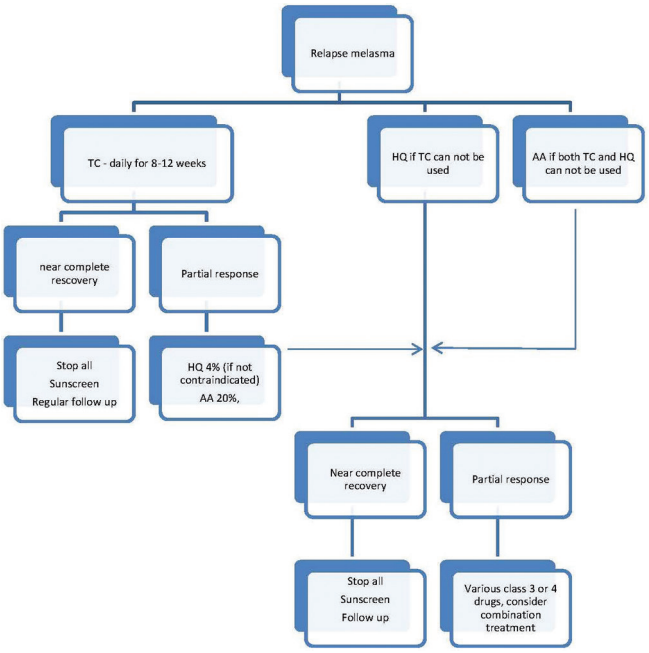

Figure 2: Step-wise management of "relapsed cases"

Second, there is the large gap between the available and required scientific evidence for the treatment of melasma. Various treatment options are available but well-designed RCTs are lacking. Due to nonhomogenous study parameters, outcome assessment and comparison is extremely difficult. Long-term safety, risk of AE, potency in comparison to the established therapies are unknown for most of the drugs. Significant lack of large studies among Indians is another hindrance to develop a therapeutic guideline for the Indians. Females largely outnumbered the males resulting in lack of evidence for the ideal therapeutic options for males.

Proposed therapeutic guideline is based on, but not exclusively dependent on, the evidence. We have considered various practical aspects while formulating the therapeutic recommendation.

Melasma is a resistant disease and relapse is a rule than a rarity. This, on the backdrop of paucity of evidence on drugs for every practical situation, treatment of this condition should not be very strictly bound by guideline. We are of opinion that the treating physician should use his/her clinical acumen to select various combinations that he/she might consider safe and effective.

It is expected that this publication with detailed evidence on melasma treatment and suggested step-wise treatment recommendation will be helpful for the physicians primarily practicing in India and other neighboring countries having people with similar ethnic origin.

Finally, this is not a legal document. Similar to all other guidelines, nonadherence to this guideline may not be considered as a negligence and adherence may not be considered as a defense to negate negligence.

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Conflicts of interest

There are no conflicts of interest.

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