Melasma: Treatment Approaches

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Acquired Disorders of Hyperpigmentation

- Post-inflammatory hyperpigmentation
- Lentigines
- Melasma
- Periorbital dark circles
- Drug-induced hyperpigmentation
- Acanthosis nigricans
- Erythema dyschromicum perstans
- Lichen planus pigmentosus
- Pigmentary demarcation lines

Visible Light May Cause Melasma

- 20 volunteers tested on back
  - Visible (400-700 nm)
  - UVA1 (340-400 nm)
- BOTH induced immediate and delayed hyperpigmentation in skin type 5
- Currently available sunscreens inadequate

Visible Light Sunscreen and Melasma

- 68 patients with MASI > 8
  - UV-only sunscreen with Mexoryl
  - UV + visible light sunscreen with iron oxide
- Application every 2-3 hrs X 8 wks
- All received HQ 4%
- Improvement in MASI
  - 77.8 ± 11% for visible group
  - 61.9 ± 16% for UV-only group
- Biopsies: Melanin significantly lower in visible group

Sunscreens with Iron Oxide May Improve Melasma

- Study with 20 subjects evaluated after ALA applied to arm
- Different sunscreens applied prior to visible blue light exposure
- Results: Minimal phototoxic dose (MPD) 18 hours post ALA

<table>
<thead>
<tr>
<th>Sunscreen</th>
<th>SPF (J/cm²)</th>
<th>Protection Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (no sunscreen)</td>
<td>0.33</td>
<td>0</td>
</tr>
<tr>
<td>B: Titanium dioxide 15%, zinc oxide 8.6%, iron oxide 3.2% (Avene compact paste, SPF 50)</td>
<td>5.78</td>
<td>21</td>
</tr>
</tbody>
</table>

Sunscreens with Iron Oxide May Improve Melasma

- Zinc oxide containing sunscreens
  - Small particles (<40 nm) provide protection mostly against UVB
  - Large particles (100 nm) provide visible light protection but sunscreen appears white and is not cosmetically acceptable
  - Tinted sunscreens containing iron oxide are capable of absorbing visible light
- Consider adding tinted iron oxide (>3%) sunscreens and makeup for patients with melasma (e.g. Avène High Protection Compact SPF 50, Femme Couture Mineral Effects Tan Pressed and Get Corrected CC Makeup)

Increased Blood Vessels in Melasma Lesions

- 50 Korean women with melasma
- Biopsy of lesional and peri-lesional skin
- ↑ vessel size and density
- ↑ in vascular endothelial growth factor (VEGF) expression by keratinocytes
- Number of vessels correlated with intensity of pigmentation


Keratinocytes in Melasma Lesions Make VEGF

- Angiogenesis may be related to VEGF expression in epidermis
- ↑ a* value by colorimetry in lesional skin, consistent with increased erythema
- Anti-angiogenesis topicals could be studied
- Vascular lasers may be of benefit


Triple Combination Cream + PDL for Melasma

- Dual treatment designed to target melanin and vasculature
- 17 patients, treated with TC cream daily for 4 months
- PDL applied every 3 weeks X 3 sessions for one side of face
- MASI scores:
  - Only phototypes II and III improved, phototype IV unchanged


IPL + TC Cream for Melasma

- 56 patients from USA treated for 10 weeks
- ½ of face treated with TC cream and ½ with control cream
- Two sessions of IPL (filter 560 nm and fluence of 14-18 J to skin phototypes II-IV) at weeks 2 and 6 to the whole face
- Creams discontinued one day before to one day after IPL
- Photos at baseline, week 6 and week 10
- 57% were clear or almost clear on combination side vs. 23% on IPL only side
- Well tolerated


Tranexamic Acid

- Plasmin inhibitor and antifibrinolytic
- FDA approval in 2009 for menorrhagia
- Over the counter in some countries (UK, Sweden)
- Also used for intraoperative and trauma related hemorrhage
- Used widely for melasma in East Asia (Japan, Korea, Singapore)
- Topical, intradermal and oral forms – latter potent and convenient


Tranexamic Acid for Menorrhagia

- Recommended oral dosage is 2 pills, 650mg each, three times daily for up to 5 days
- Max total dose of 20g/month (dose for melasma: 15 g/month)
- Contraindications
  - Active thromboembolic disease
  - History of thrombosis or thromboembolism
  - Intrinsic risk for thrombosis or thromboembolism
- Pregnancy category B drug

Retrospective Review of Tranexamic Acid in 561 Patients With Melasma

- Retrospective review of 561 patients in Singapore
- 91% female
- Dosed at 250 mg bid
- 91.7% improved
- Mean response in 2 months
- 7.1% with adverse effects
- 1 thrombotic event in a patient with protein S deficiency and a family history of thrombotic events who withheld history and developed a DVT
- Better results in those with older age of onset and longer duration of disease

Chee Leok Goh, MD, MRCP et al. JAAD May 2016

Summary - Tranexamic Acid for Melasma

- Over 12 studies (> 1600 patients) published, all from Asia, all but one uncontrolled
- Dose is usually 250 mg bid (lower than menorrhagia dose)
- Treatment duration 1-4 months
- Causes moderate improvement, based on MASI scoring
- Side effects are rare
- Contraindications: history of deep venous thrombosis, stroke, other thrombotic events, hypercoagulable states, use of anticoagulants, ≥ 2 or more spontaneous abortions, pregnancy, nursing
- Relative contraindications: family history of DVT

Principles of Melasma Therapy

- Protection from sun exposure
- Inhibition of tyrosinase activity
- Removal of melanin
- Destruction or disruption of melanin granules


Treatment of Melasma

- Sunscreens
- Cosmetics
- Discontinuation of OCP’s
- Tyrosinase inhibitors
  - Hydroquinone
  - Kojic acid
  - Arbutin and deoxyarbutin
  - Liquorice extract (liquiritin)
  - Bearberry (arbutin)
  - Deoxyarbutin


- Stimulation of keratinocyte turnover
- Reduction in melanosome transfer
- Inhibition of protease activated receptor 2
- Inhibition of plasmin
- Glycolic acid
- Lactic acid
- Trichloracetic acid
- Pyruvic acid
- Salicic acid
- Jessner’s solution
- Laser surgery
- Paper mulberry extract
Hydroquinone vs. Placebo for Melasma

- 48 patients in Brazil treated with 12 weeks of 4% HQ or placebo bid, along with sunscreens
- 40% of HQ group, and 10% of placebo group had "total improvement"
- 57% of HQ group, and 58% of placebo group had partial improvement
- Subjective evaluation methods


Hydroquinone

- 5% much better than 2%
- > 15 million tubes containing HQ sold each year in the USA
- 5-10% formulas frequently compounded by dermatologists
- Penetration MAY be increased with tretinoin and glycolic acid
- Response in 4-6 weeks, maximum in 3-6 months or longer
- Irritation and ochronosis rare
- Exogenous ochronosis more common with high concentrations, lack of supervision or combination with resorcinol


Fluocinolone acetonide 0.01%, Hydroquinone 4%, Tretinoin 0.05% (Tri-luma) Cream

- Stable, high quality variant of the Kligman/Willis Formula
- Contains class 6 corticosteroid (previously pediatric Synalar)
- Longer shelf life than compounded formulations
- Two 8-week multicenter, randomized, investigator blind active control trials
  - Triple combination Cream compared to RA+HQ; RA+FA; HQ+FA
  - Trials encompass 13 study centers
  - 641 patients enrolled, 603 assessed


Week 8 Results: Patients with Melasma Severity Score of 0 or 1

- Study 1 (N=338)
  - 85.9% Tri-Luma FA&HQ
  - 49.4%* FA&RA
  - 27.1%* RA&HQ
  - 61.4%* Study 2 (N=303)
  - 67.1% Tri-Luma FA&HQ
  - 34.2%* FA&RA
  - 27.6%* RA&HQ
  - 30.7%*

Adverse Events: Combined Results

<table>
<thead>
<tr>
<th></th>
<th>TC cream N=161</th>
<th>RA+HQ N=158</th>
<th>FA+RA N=161</th>
<th>FA+HQ N=161</th>
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<tbody>
<tr>
<td>Pts w/ at least one AE</td>
<td>75%</td>
<td>87%</td>
<td>81%</td>
<td>59%</td>
</tr>
<tr>
<td>Application site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>41%</td>
<td>44%</td>
<td>26%</td>
<td>16%</td>
</tr>
<tr>
<td>Desquamation</td>
<td>38%</td>
<td>61%</td>
<td>22%</td>
<td>4%</td>
</tr>
<tr>
<td>Burning</td>
<td>18%</td>
<td>23%</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>Dryness</td>
<td>14%</td>
<td>13%</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11%</td>
<td>22%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Atrophy</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>


Preventing Recurrence of Melasma with TC Cream

- Randomized, investigator blinded, controlled study
- 242 patients with melasma enrolled in 16 centers in Brazil and Mexico
- Those attaining clear or mild disease after 8 weeks of daily TC cream went into maintenance phase X 6 months
- Subjects randomized to receive TC twice weekly or a tapering regimen (3 X week for 1 month, 2 X per week for 2 months and once per week for 4 months)
- 78.8% entered maintenance phase
- After 6 months, 53% remained relapse-free
- Time to relapse was similar between groups
- Prevented recurrence of melasma

Arellano I, et al. JEADV 2012; 26: 611–618
Preventing Recurrence of Melasma with TC Cream

- Melasma severity at study entry, not maintenance baseline, influenced relapse rate
- The twice weekly regimen tended to show better effectiveness in postponing relapse in severe melasma
- Both regimens were safe
- QOL improved in those with improvement in melasma
- Irritation was treated by holding the TC cream for a few days and then using a moisturizing cream prior to applying the TC cream

Arellano I, et al. JEADV 2012; 26: 611-618

Atrophogenic Potential of Triple Combination Cream

- 60 patients with melasma treated with triple combination cream once daily for 12 weeks, majority Latino women
- If clear or almost clear at 12 weeks, patients entered maintenance phase, applying cream twice weekly for 12 weeks
- If relapse occurred, patients resumed daily treatment until end of study at 24 weeks
- If not clear or almost clear at 12 weeks, patients continued daily therapy for 12 weeks
- Biopsies of involved skin taken at baseline, 12 weeks and 24 weeks and compared to biopsy from uninvolved skin


Tretinoin, Hydroquinone, and Topical Steroids (Kligman/Willis Formula)

- Dexamethasone 0.1%, hydroquinone 5%, tretinoin 0.1%
- Proposed mechanisms of action:
  - Tretinoin reduces atrophogenic effects of steroid, facilitates epidermal penetration of hydroquinone and reduces melanosome transfer
  - Steroid helps reduce irritation from tretinoin and decreases pigmentation on its own
  - Daily application X 5-7 weeks resulted in complete lightening
  - Results significantly less favorable if any one component was omitted
  - No cases of atrophy were seen

Kligman AM, Willis I. Arch Dermatol 1975;111:40-48

Hydroquinone, Tretinoin, Steroids

- All 3 have a depigmenting effect
- A variety of formulations have been used

<table>
<thead>
<tr>
<th>Hydroquinone</th>
<th>Tretinoin</th>
<th>Topical Steroid Cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>0.05%</td>
<td>Dexamethasone Val 0.1%</td>
</tr>
<tr>
<td>4%</td>
<td>0.05%</td>
<td>Triamcinolone 0.01%</td>
</tr>
<tr>
<td>5%</td>
<td>0.1%</td>
<td>Dexamethasone 0.1%</td>
</tr>
<tr>
<td>8%</td>
<td>0.05%</td>
<td>Trimecinoine 0.05%</td>
</tr>
<tr>
<td>2-8%</td>
<td>0.03125%-0.1%</td>
<td>Hydroquinone, Desonide, Triamcinolone, Trimecinoine, Dexamethasone, Pimecrolimus</td>
</tr>
</tbody>
</table>


Abuse of Depigmenting Creams

- Chart review of 69 Indian patients
- Unsupervised, intermittent usage was common
- High potency CS commonly used
- Side effects
  - Erythema: 43
  - Hypertrichosis: 30
  - Tachyperpigmentation: 25
  - Asymetric hypopigmentation: 18
  - Rosacea-like eruption: 18
  - Contact-like depigmentation: 8
  - Eosinophilic spongiosis: 6
  - Irritant dermatitis: 1

Kandhari R, Khunger N, Indian J Dermatol Venereol Leprol 2013

Azelaic Acid in Melasma

- Naturally occurring dicarboxylic acid
- 20% azelaic acid equivalent to 4% hydroquinone in a 24-week double blind study of women from S. America
- 20% azelaic acid found to be significantly better than 2% hydroquinone in 132 Filipino women treated for 6 mos (Verallo-Rowell et al, 1989)


Verallo-Rowell VM, et al., Acta Derm Venereol (Stockh) 1989; 143(suppl):58
Kojic Acid in Melasma

- Tyrosinase inhibitor
- 39 patients, treated with kojic acid 2% gel on one side of face and 2% hydroquinone gel on the other side bid for 3 mos.
- 5% glycolic acid in both formulations
- Clinical evaluation plus UV photos
- 51% responded equally, 28% KA better, 21% HQ better
- Mean decrease in pigment intensity was 58%
- Several had to change to qod frequency due to irritation


Glycolic Acid Peels + Modified Kligman’s Formula for Melasma

- 40 women from India treated with serial peels + modified Kligman’s formula (MKF) vs. MKF alone for 5 months
- MKF: 2% HQ + 0.05% tretinoin cream + 1% hydrocortisone cream
- Six serial glycolic acid (GA) peels to half the patients every 3 weeks
- First 3 peels 30% GA and last 3 peels 40% GA
- Maximum time of contact was 3 minutes
- Subjective scoring methods
- Improvement in MASI

<table>
<thead>
<tr>
<th></th>
<th>Peels + MKF</th>
<th>MKF alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>45.9%</td>
<td>33.2%</td>
</tr>
<tr>
<td>21 weeks</td>
<td>80%</td>
<td>63.1%</td>
</tr>
</tbody>
</table>
- Tolerated well


Randomized, Split-Face, Investigator Blinded, Controlled Trial with Glycolic Acid Peels for Melasma

- 20 Hispanic women
- Twice daily 4% hydroquinone
- Four serial glycolic acid peels to one side of the face every 2 weeks
- First 2 peels 20% GA and last 2 peels 30% GA
- Results:
  - Both sides improved significantly
  - Both Mexameter and MASI scores showed NO SIGNIFICANT DIFFERENCE between both sides

Hurley ME, Pandya AG, et al., Arch Dermatol 2002; 138:1578

Randomized, Split-Face, Investigator Blinded, Controlled Trial with Salicylic Acid Peels for Melasma

- 20 patients
- Hydroquinone 4% cream to both sides of face
- Four salicylic acid peels, once every 2 weeks to one side of face
- First 2 peels: 20% SA, second two peels -30% SA
- 8 week follow up period
- Results:
  - Both sides improved
  - Both Mexameter and MASI scores showed NO SIGNIFICANT DIFFERENCE between both sides

Kodali S, Pandya AG, et al, JAAD, 2010; 63:1030-1035

70% GA Peels vs. Nanosome Vitamin C Iontophoresis

- 14 women from Egypt, skin types 4-6
- 70% GA on right side of face, nanosome vitamin C by iontophoresis to the left side
- Peel applied for 1-3 minutes or until patients felt burning
- 0.5 ml liposomal Vit C applied for 10 minutes using iontophoresis machine
- Total of 6 sessions, unknown frequency
- Results were modest and better with Vit C iontophoresis

Sobhi RM, Robhi AM, J Cosm Dermatol 2012

Microdermabrasion for Melasma

- 27 year-old LAF
- Melasma for several years
- Microdermabrasion twice, 2 weeks apart, at FP clinic
- No. of microdermabrasion passes and machine type unknown
- Presented 6 weeks after second procedure
Non-ablative 1550-nm Fractional Photothermolysis (NFP)

- 51 patients with melasma, skin types 2-3 (Germany)
- ½ received broad spectrum sunscreen alone (BP200; Daylong® extreme)
- ½ received sunscreen + treatment with NPF every 3 wks X 4
- Dosing: 1550-nm NFP treatment (15 mJ/microthermal zone (MTZ); total density: 1048 MTZ/cm²; density per pass: 131 MTZ/cm²; number of passes: 8; total coverage: 20%)
- Evaluation at baseline and 12 weeks after final treatment
- Outcome measures: MASI and PGA
- MASI improvement: Laser group - 27%, Control group - 31%
- No difference between two groups

Kersal E, et al, JEADV 2012; 26:470-476

Low-fluence Q-switched Nd:YAG laser for melasma in Asians (Laser Toning)

- Split-face study: Q-switched Nd:YAG laser + 2% hydroquinone vs. 2% hydroquinone alone
- Parameters: 1,064-nm Q-switched Nd:YAG laser, 6-mm spot size, 3.0- to 3.8-J/cm² fluence (sub photothermolytic)
- One pass every week for 5 weeks
- Results: 93% colorimeter and 76% MASI improvement on laser side compared to 20% and 24%, respectively, on control side
- 12 weeks follow up, 4/22 patients had rebound hyperpigmentation and there was at least mild recurrence of melasma in all patients despite use of 2% HQ and sunscreens
- Mottled hypopigmentation in 4 patients with darker skin (type V)


Melasma Treatment Algorithm

Acute
- Hydroquinone
- Triple combination cream
- Compounded cream
- Tranexamic acid
- Peels?
- Laser?

Maintenance
- 2% hydroquinone
- Triple combination cream
- 2-3 X per week
- Kojic acid
- Azelaic acid
- Arbutin
- Combination

Conclusions

- Rule out other causes of facial pigmentation
- Dermatologists must know how to critically interpret studies
- Sunscreens against UVA and UVB are critical for success
- Sunscreens against visible light may also be important
- Hydroquinone is still the most effective depigmenting agent
- Triple combination cream is effective in the majority of patients
- Tranexamic acid shows promise in treating melasma without significant side effects
- Close follow-up of patients is important to avoid side effects
- Most patients need long-term treatment