Interventions for melasma
Overview

- Melasma – who what where why?
- Evidence for what treatments work- Cochrane review
- New key trials
- My practice and pitfalls
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What is Melasma?

• Acquired, chronic recurrent hyperpigmentation of the skin

• Characterised by symmetrical light to dark muddy brown macules and patches mostly on the areas of the face exposed to the sun, such as the cheek bones, forehead, and chin
Who is affected?

- More common in women

- Prevalence of melasma ranges from 8.8% in Latino females in Southern US to as high as 40% in Southeast Asian populations.

- A survey of 2000 Afro Carribean participants in Washington found melasma to be the third most common pigmentary disorder of the skin.

- A multicenter survey of females from 9 countries found that Fitzpatrick skin phototypes III and IV were most commonly affected.
Why melasma occurs?

- UV light, is commonly reported initiating or exacerbating factor. Patients report increased severity of melasma with sun exposure.

- Genetic predisposition - high reported incidence in family members in several studies but the exact risk is unknown.

- Hormonal link to melasma - Many patients note onset or worsening with pregnancy or oral contraceptives. Studies report 5-50% of patients identified pregnancy as a triggering factor.

- Thyroid disorders and stress
Overview

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Interventions for melasma

- Assess treatments to limit or reduce melasma and prevent recurrence

- No language restriction

- Published and unpublished RCTs relating to the treatment of melasma

- Open label trials (placebo use possible) were included if assessment was done blindly

- Open label trials (placebo use not possible) included if assessment was done blindly OR objective measures used

- Patient assessed change in melasma severity and QOL
- Physician assessed change, Side effects
Summary findings

- Included 20 studies
- 2125 participants
- 23 different treatments

- Azelaic acid (2) - Balina 1991b; Sivayathorn 1995
- Topical retinoid (3) - Griffiths 1993; Kimborough-Green 1994, Leenutaphong 1999
- Combination creams (6) - Espinal Perez 2004; Chan 2008; Taylor 2003; Guevara 2003; Lim 1997; Lim 1999
- Combination therapies (4) - Hurley 2002; Lim 1997; Wang 2004; Ejaz 2008
- Less conventional therapies (4) - Khemis 2007; Huh 2003; Thirion 2006; Franscisco Diaz 2004
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WHAT FORMULATION OF HYDROQUINONE TO USE?
What formulation of hydroquinone to use?

- The formulation of hydroquinone used was mostly 4% hydroquinone cream

- All trials using hydroquinone compared 2 active interventions.
Physicians assessed improvement according to one of three categories: total improvement, partial improvement, or failure.

48 Participants with melasma
4% hydroquinone and 2 sunscreens with SPF 15 bd
SPF-30 sunscreen every morning
2 sunscreens with SPF-15 bd
SPF-30 sunscreen every morning
12 weeks

Ennes 2000
Cointervention

• Physicians assessed improvement according to one of three categories: total improvement, partial improvement, or failure.
• Statistically significant difference between the groups in favour of HQ and sunscreen. (authors report $P = 0.0082$ - unclear which category of improvement analysed)

• This significant difference between the groups evident from week 3.

• No difference in tolerability. Adverse events eg. mild erythema (RR 1.37, 95% CI 0.49 to 3.85). No serious adverse events
4% Hydroquinone - Conclusion

- Hydroquinone 4% is a safe and effective for the treatment of melasma and that sunscreens are important as concomitant treatment by way of preventing repigmentation.

- One outcome measure and incomplete
- well tolerated
- early onset of action- week 3
WOULD COMBINING HYDROQUINONE WITH ANOTHER TREATMENT BE MORE EFFECTIVE?
11/18 participants felt there was more improvement on the peeled side versus 4/18 on the non-peeled side. One of the 18 felt there was no difference between the 2 sides.

- Missing data on two participants
Evidence for 4% Hydroquinone + Peels

- On the physician evaluation, there was a significant improvement from baseline in both groups there was no significant difference between the sides in terms of objective mexameter reading or subjective MASI scores.

- Four participants developed significant erythema though no peeling or erosions occurred secondary to the peels.
Authors concluded that 4% hydroquinone is effective in the treatment of melasma but the addition of 4% glycolic acid peels did not enhance the effect of hydroquinone.

- Incomplete data on participant outcomes
- Sponsored by ICN pharmaceuticals manufacture peels and creams
Evidence for 4% HQ + Intense Pulse Light

Wang 2004

Cointervention

- The frequency of hydroquinone application in either group is unclear.

- The rationale for hydroquinone in the control arm where participants had been shown to be unresponsive is also unclear.
• On objective measures, there was a greater reduction in the melanin index score in the hydroquinone and pulsed light group ((39.8% in HQ+IPL versus HQ group 11.6% authors report P < 0.05).

• Adverse events were noted in the IPL group- mild erythema and pain, microcrust for 1-2 weeks, 2 patients with PIH settled with HQ.
4% HQ + Intense Pulse Light- Conclusion

- Authors concluded that IPL is safe and effective treatment for refractory melasma with minimal side effects.

- No frequency of HQ and if same between groups

- 2/17 post inflammatory hyperpigmentation in the IPL group
ARE THERE ALTERNATIVES AT LEAST AS EFFECTIVE HYDROQUINONE?
• There was a large loss to follow up (86 participants). Differential loss to follow up not significant. Assessments performed on 122 participants in the azelaic acid and 121 participants in the hydroquinone group.
20% Azelaic acid vs 4% Hydroquinone

- Physicians rated 71.9% of those in the hydroquinone group as good/excellent response versus 64.8% in the azelaic acid group (RR 1.11, 95% CI 0.94 to 1.32;).

- On the objective measure of reduction in lesion size, no significant difference was demonstrated.

- Side-effects (local irritation) were mild occurring more frequently in the azelaic acid group (18/122) versus the hydroquinone group (1/121 allergic sensitisation) (RR 17.85, CI 2.42 to 131.64;)

20% Azelaic acid vs 4% HQ - Conclusion

- No significant differences between 20% azelaic acid and 4% HQ. Severe side effects did not occur with azelaic acid.

- Large loss to follow up (26%)
- Local irritation in 18/122 azelaic acid
- Sponsored by Schering AG, Berlin - unclear if they manufacture study creams
Physicians rated significantly more participants in the azelaic acid group (75.5%) as having a good/excellent response compared to 2% HQ group (47.1%).

No statistically significant difference between the groups on objective measure of reduction in lesion size.

Itching, burning, and erythema in 76/147 in the azelaic acid group and 24/153 in the HQ group. (RR 3.3, 95% CI 2.21 to 4.91)
20% Azelaic acid vs 2% HQ - Conclusion

- 20% Azelaic more effective than 2% HQ on some measures comparable on others.

- Confirms the side effect profile of Azelaic acid, irritation in 76/153 vs 23/153

- Lower strength of HQ may be less effective
ARE THERE ANY TOPICALS MORE EFFECTIVE THAN HQ?
The physicians rated a higher proportion of participants in the hydroquinone and sunscreen group (96.3%) as improved compared to the hydroquinone-only group (80.8%).
Participant subjective evaluation of improvement

<table>
<thead>
<tr>
<th></th>
<th>3% HQ + sunscreen</th>
<th>3% HQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked improvement</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Slight improvement</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Worse</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>27</strong></td>
<td><strong>26</strong></td>
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</tbody>
</table>

- 9 participants unclear which arm.
Although no statistical analysis was conducted, the trial authors concluded that hydroquinone is the mainstay of therapy and addition of a sunscreen has a positive effect.

-Only study to evaluate the effect of sunscreen on melasma

-Incomplete data eg 6 patients lost to follow-up- unsure which group

-Neutrogena and Herbert laboratories supplied study creams
On participant reported outcomes, significantly more participants (71%) in the triple-combination group versus 50% in the hydroquinone group were satisfied or very satisfied (trial authors report P = 0.005).

Chan 2008

8 weeks

Triple combination cream
(fluocinolone acetonide 0.01%, HQ 4%, tretinoin 0.05%) vs 4% HQ

Cointervention
This significant difference was also reflected in the physician assessment. More participants in the TC group achieved score of 0 (none) or 1(mild) on melasma severity scale. Authors stated P < 0.001.

Early onset of action with significant differences in the score evident at week 4.

More patients had related adverse events on TC (63/129, 48.8%) than on HQ (18/131, 13.7%) but most were mild (erythema, irritation and discomfort) and none severe.
Efficacy in Asians and patient satisfaction were superior with TC than with HQ 4%

- Patient satisfaction assessed
- Early onset of action, though half of patients had side effects (48.8% versus 13.7%)
- Sponsored by Galderma manufacture TCC, 2 authors employees of Galderma
DO YOU NEED ALL THREE INGREDIENTS IN TRIPLE COMBINATION CREAM?
641 participants
Moderate to severe melasma

Triple combination cream vs Dual combination agents

Taylor 2003

8 weeks
Triple combination cream vs Dual combination agents- Conclusion

• Triple combination was significantly more efficacious compared to each dual combinations on physician subjective evaluation

- Study design was complex- Pooled data ? Homogenous

- Confirms that side effect profile of TC seen in 63% (erythema, desquamation, burning)

- Sponsored by Galderma
ARE THERE ANY OTHER ALTERNATIVE TREATMENTS?
• 94% epidermal, 4% dermal, and 2% mixed melasma.

• At 40 weeks there was significant difference favouring tretinoin on physician assessed subjective measures and objectively with colorimetry.
Evidence for 0.1% Tretinoin cream

- The onset of improvement is slow. First significant improvement occurred at 24 weeks of tretinoin treatment.

- Moderate redness and peeling noted in 22/25 tretinoin participants. In a further five tretinoin participants the reaction was severe.
0.1% Tretinoin cream- Conclusion

- Topical 0.1% tretinoin produces significant clinical improvement of melasma, mainly due to reduction in epidermal pigment, but improvement is slow.

- Study with longest duration.

- Numbers of side effects confusing nonetheless moderate/severe side effects in all patients.

- W. Johnson Pharmaceutical research institute, NJ but no part in design or conduct of study and Babcock dermatologic endowment, Michigan, USA.
2. Evidence for 0.1% Tretinoin cream

Kimborough Green 1994

- 43% epidermal, 37% dermal, and 20% mixed melasma.
- 2 subjective measures. No significant difference on the scale of much worse to much improved, there was significant difference in mean reduction of MASI score (32% in tretinoin group vs placebo 10%, P = 0.03).
- The significant improvement was also confirmed on colorimetry (the trial authors report P = 0.02).
• More adverse events in tretinoin group with mild erythema and/or peeling in 10/15 participants versus 1/15 in the placebo group (RR 10.0, 95% CI 1.46 to 68.69).

- Long duration. Efficacy in dermal melasma. (some not all measures)

- Confirms side effects

- RW Johnson Pharmaceutical research institute but no part in design or conduct of study and Babcock dermatologic endowment, Michigan, USA
Omissions

- Less conventional therapies - Rucinol serum, Vitamin C, iontophoresis, Thiospot, Gigawhite
- Combination creams -
  - HQ+Glycolic acid+ Vit C+ Vit E+ sunscreen
  - HQ+ Glycolic acid+ kojic acid
  - HQ+Glycolic acid
- Isotretinoin gel
- Jessners peel/ Salicylic acid peel
- 5% L ascorbic acid
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Preventing melasma recurrence
Preventing melasma recurrence: prescribing a maintenance regimen with an effective triple combination cream based on long standing clinical severity

- In both arms 53% remained relapse free (53.8% in twice weekly vs 53% in tapering regimen). Time to relapse was similar in both groups (mean 190 days)

- Side effects (redness and irritation) 10.9% in tapering vs 12.2% in twice weekly. 1 patient had atrophy in the twice weekly group, 6 telangectasia

- After resolution of melasma, maintenance therapy over 6 months could prevent recurrence in over half of patients

- No information on previous treatment. Primary outcome - MASI

- The median increase in MASI from baseline to month 6 was significantly higher with formula B (no visible light protection) compared to formula A (P=0.027)

- Sunscreen with UVA/UVB and visible light filters are more protective against relapses than sunscreen without visible light protection
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Aggravating factors
- UV + visible light
- Hormonal

Treatment

Recurrence
Is the diagnosis melasma?

Aggravating factors:
- UV + visible light
- Hormonal

Treatment

Recurrence
Is the diagnosis melasma

Aggravating factors
- UV + visible light

Treatment

Recurrence

Early/epidermal melasma - tretinoin, lower strengths, Side effects, long term treatment. Moisturiser

Mixed/dermal melasma - Triple combination cream 2 months, Side effects, moisturiser

Azelaic acid - Side effects

4% HQ
Is the diagnosis melasma

Aggravating factors
- UV + visible light
- Hormonal

Treatment

Recurrence
Thank you

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