Systematic review of randomized controlled trials on interventions for melasma: An abridged Cochrane review

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See related articles on pages 281 and 352

Background: Multiple treatments exist for melasma; they are often substandard and associated with side effects.

Objectives: We sought to assess the effectiveness of interventions used in the management of all types of melasma.

Methods: We undertook a systematic review using the methodology of the Cochrane Collaboration.

Results: We included 20 studies with a total of 2125 participants covering 23 different treatments. A meta-analysis was not possible because of the heterogeneity of treatments. Triple-combination cream (hydroquinone, tretinoin, and fluocinolone acetonide) was more effective at lightening melasma than hydroquinone alone (relative risk 1.58, 95% confidence interval 1.26-1.97) or any of the agents in a dual-combination cream. Azelaic acid (20%) was significantly more effective than 2% hydroquinone (relative risk 1.25, 95% confidence interval 1.06-1.48) at lightening melasma. In 2 studies where tretinoin was compared with placebo, objective measures demonstrated significant reductions in the severity. However, only in 1 study did participants rate a significant improvement (relative risk 13, 95% confidence interval 1.88-89.74).

Limitations: There was poor methodology, a lack of standardized outcome assessments, and short duration of studies.

Conclusions: The current limited evidence supports the efficacy of multiple interventions. Randomized controlled trials on well-defined participants with long-term outcomes are needed. (J Am Acad Dermatol 2014;70:369-73.)

Key words: ascorbic acid; azelaic acid; chloasma; glycolic acid; hydroquinone; melasma; pigment; tretinoin; triple combination; vitamin C.

Treatments for melasma can be broadly classified into topical preparations, laser, or other therapies. Outcomes are variable and may be associated with side effects such as irritation and scarring.

The objectives of this study were to assess the effectiveness of interventions to treat melasma and avoid recurrence; investigate whether factors such as race, sex, and skin color had effect on treatment response; determine the incidence of

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adverse reactions; and identify the need for further studies.

METHODS

This study was based on a published protocol in accordance with the methodology of the Cochrane Collaboration.[1,2] We carried out a systematic review of randomized controlled trials (RCTs) on interventions for melasma.[3]

Outcome measures

The primary outcome measured was participant-assessed response of impact on quality of life and participant-assessed changes in melasma severity. Secondary outcome measures included physician-assessed changes in melasma severity, through subjective and objective evaluation, and time needed for improvement of melasma. Further secondary outcomes included adverse events and long-term remission rate (>12 months).

Search strategy

We searched 6 electronic databases on May 25, 2010 and 5 trial registers on June 1, 2009 (Table I). We checked the references of included and excluded studies for potential references to further RCTs. No language restrictions were imposed and where necessary translations were undertaken.

Data collection and analysis

Two authors (R. R. and J. H.) independently assessed each study to determine whether it met the predefined selection criteria. Using a piloted data extraction form, each trial was summarized. We contacted trial authors for missing data. The risk of bias and the methodological quality were assessed as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[2] The main aspects are listed in Table II. The variety of therapies assessed and the heterogeneity of studies precluded quantitative pooling of data. Of the included trials only half had participant-reported outcomes.

RESULTS

Description of studies

Of the 257 citations from our search, 20 RCTs met our inclusion criteria, with a total of 2125 participants covering 23 treatments.[4-23] All studies included adult participants and 12 studies had only female participants. Four studies included only epidermal melasma, 7 studies included epidermal and mixed melasma, 4 studies included all types of melasma, and in 5 studies the type of melasma was not specified. Of the 20 RCTs included, 7 of them were right-left comparisons and a further 7 were placebo controlled. The quality of studies evaluating melasma treatments was generally poor (Fig 1) and available treatments inadequate.

CAPSULE SUMMARY

- Melasma presents a treatment challenge.
- The current limited evidence supports the efficacy of multiple interventions.
- The evidence from this review is insufficient to provide clear guidance for clinical practice. Further randomized controlled trials on well-defined participants with long-term outcomes are needed.

DISCUSSION

The large number of different treatments evaluated shows that there is no standard therapy for melasma. The evidence supporting any particular intervention is weak. No meta-analysis was possible because of the clinical heterogeneity of the treatments. It is also worth noting that most included trials compared 2 or more active treatments and consequently the relative risk reported may be lower than if placebo-controlled trials were conducted. In addition, some studies may have failed to reach statistical significance for this same reason and care has to be exercised in not concluding that none of the treatments work.

Single treatments

Topical hydroquinone was the most common intervention in included trials, the 4% formulation used most frequently. All 7 RCTs using hydroquinone compared 2 active interventions. In general, trials suggest that hydroquinone (3%-4%) has a role in the treatment of melasma. Physicians found no significant difference in skin lightening between hydroquinone (4%) compared with 20% azelaic acid and with 5% ascorbic acid in separate trials. The participants, however, in the ascorbic acid trial found a significant difference in favor of hydroquinone.[4,8] Hydroquinone when used as a lower strength of 2% was not as effective as 20% azelaic acid according to physician assessment.[19]

Tretinoin appears to be more effective than placebo in lightening melasma by objective measures in those with light and dark skin.[10,15] In both trials a co-intervention of sunscreen of a least sun-protection factor 15 was used. There appears to be no difference between topical isotretinoin and placebo.[16]

Four RCTs also suggest some efficacy of unconventional therapies. Thiospot (SkinMed, North Yorkshire, UK) appears more effective at lightening

Table I. Electronic databases and trial registers searched

Cochrane Skin Group Specialized Register (from inception to present)
Cochrane Central Register of Controlled Trials (from inception to present)
MEDLINE (2004 to present)
EMBASE (2006 to present)
LILACS (Latin American and Caribbean Health Science Information database) (from inception to present)
PsychINFO (from inception to present)
Trial registries (from inception to present)
metaRegister
US National Institutes of Health ongoing trials register
The Australian and New Zealand Clinical Trials Registry
The World Health Organization International Clinical Trials Registry platform
The Ongoing Skin Trials register

Table II. Quality assessment of included studies

1) Method of randomization
2) Allocation concealment
3) Blinding
4) Incomplete outcome data
5) Intention-to-treat analysis
6) Comparability of the 2 treatment groups in each arm

melasma compared with placebo as does Rucinol serum (Pola Chemical Industries, Inc, Tokyo, Japan).[14,21] Vitamin-C iontophoresis appears significantly more effective than distilled water iontophoresis on objective assessment, although the participants in the study could not tell the difference.[12] Similarly, in the trial of a botanical extract, Gigawhite (Dutch State Mines, Alpaflor, The Netherlands) 5%, no significant differences to placebo were seen on subjective assessment by the physicians, although colorimeter analysis showed that the side treated with Gigawhite was significantly lighter.[9]

Combination therapies

Hydroquinone was not effective as a triple-combination cream (hydroquinone, tretinoin, and steroid) or as effective as when combined with intense pulsed light treatment.[5,23] When hydroquinone cream was compared with combination therapy of hydroquinone and glycolic acid peels, no significant difference was found between them. There was a significant improvement from baseline in both cohorts.[13] Hydroquinone's (3%) depigmentation capability is augmented when combined with a daily sunscreen.[22]

Some combination creams clearly have a role in the management of melasma. Hydroquinone, tretinoin, and steroid seem more effective than any of the agents in a dual-combination cream.[20] In addition, hydroquinone and sunscreen appear more effective than sunscreen alone as does the combination of hydroquinone, glycolic acid, vitamins, and sunscreen compared with sunscreen alone.[7,11] There seems to be no differences between hydroquinone, glycolic acid, and kojic acid cream versus hydroquinone and glycolic acid cream, or between hydroquinone and glycolic acid versus a combination of hydroquinone, glycolic acid cream, and glycolic acid peels.[17,18] No difference appears to exists between Jessner peel and salicylic acid peels both with tretinoin priming.[6]

Conclusions

Unfortunately, poor design has hampered these studies and as such no distinct inference can be made as to a truly effective treatment for melasma. The lack of replication of the studies limits the overall applicability of results. No studies provided long-term effects of the interventions and quality-of-life data. Furthermore, a substantial number of studies failed to incorporate participant assessment (our primary outcome measure). All RCTs assessed therapies aimed at depigmenting melasma rather than approaches such as cosmetic camouflage, laser therapy, or preventative measures such as sunscreen. Eleven of the included studies were industry sponsored; there is evidence to suggest that only positive studies are likely to be reported.[24]

Implications for practice

The evidence from this review is insufficient to provide clear guidance. All interventions, except tretinoin, were evaluated in 1 study each. Tretinoin is beneficial in both lighter- and darker-skinned participants. Triple-combination cream may be more effective than hydroquinone alone or when compared with any individual constituents as a dual combination. Sunscreen alone is not as effective as sunscreen combined with hydroquinone or hydroquinone combined with glycolic acid, vitamins, and sunscreen. Hydroquinone cream combined with intense pulsed light may be more effective than hydroquinone alone. Rucinol serum and Thiospot may also be useful. The evidence in favor of vitamin-C iontophoresis and Gigawhite botanical extract is less clear. Equally the trials comparing 4% hydroquinone with 5% ascorbic acid, and 20% azelaic acid with 2% hydroquinone did not produce evidence of significant differences between the interventions.

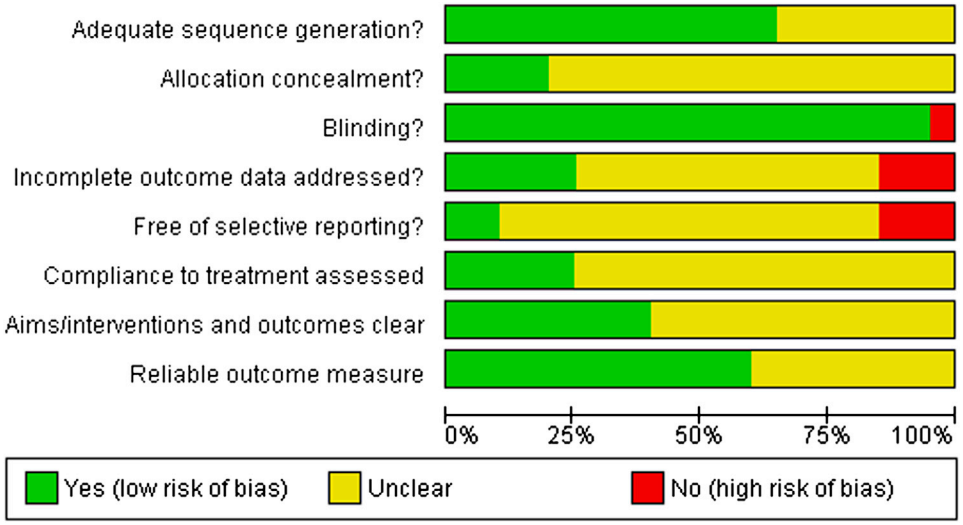


Fig 1. Methodological quality of the included studies.

Implications for research

The current evidence is extremely limited and further research with better methodological quality is required. We recommend trials have at least 6 months of intervention and at least a 12-month follow-up duration to assess maintenance. Future trials should define participants at baseline, noting age, duration of melasma, pigment type of the individual, and, using Wood's lamp, type of melasma. In addition, RCTs investigating the benefit of sunscreen are needed. If sunscreen is recommended as a co-intervention there should be details on the sun-protection factor and frequency of application, and it should be provided to participants. Trials should include quality-of-life measures developed for patients with melasma, such as the Dermatology Quality of Life Index, which will allow comparisons to be made between trials and improve relevance. Spectrometry or photography could also be used as an objective measure for the same reasons.

Finally, trials should include a more systematic approach to adverse event reporting such as participant grading of the severity and attempts should be made to establish the relationship between the adverse event and the study product.

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