Is Topical Zinc Effective in the Treatment of Melasma? A Double-Blind Randomized Comparative Study

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BACKGROUND AND OBJECTIVES Zinc plays a role in skin health, and preliminary data have shown its beneficial effects for melasma. We compared the effect of topical zinc with that of hydroquinone as the standard treatment on severity of melasma.

PATIENTS AND METHODS Ninety-three women with melasma were randomized to receive zinc sulfate 10% or hydroquinone 4% solutions once daily for 2 months. They were followed for an additional 3 months while using sunscreen. The severity of melasma was assessed at baseline and at 2 and 5 months using the Melasma Area and Severity Index (MASI).

RESULTS Eighty-two patients completed the study. The MASI score fell significantly in both groups, but a greater decrease was seen in those who received hydroquinone (43.5 $\pm$ 15.5% vs 18.6 $\pm$ 20.8%, $p < .001$). Postinflammatory pigmentation occurred in 5.2% of the zinc group and irritation in 30.9% of the hydroquinone group.

CONCLUSION Topical zinc therapy is not highly effective in reducing the severity of melasma, but further trials are needed to determine whether adding zinc to current topical treatments could improve treatment response.

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Melasma is one of the most common and disturbing cosmetic disorders with skin darkening. Pigmentation is brown to gray and usually affects the cheeks, forehead, nose, and upper lip. Melasma is more common in women; other known risk factors are pregnancy, sun exposure, and some medications such as hormones and antiepileptic medication.[1] It is more common in Asian population than in other races.[2] In Iran, there have not been enough population based studies to determine the prevalence of melasma, although Moin and colleagues reported a prevalence of 15.8% for melasma in pregnant women.[3]

Current treatments have not been successful at completely correcting the skin pigmentation of melasma.[4] Suggested medications include sunscreen, bleaching creams (e.g., hydroquinone (HQ)), acne creams (e.g., azelaic acid), and topical retinoids alone or in combination.[4,5] Other suggested treatment strategies are lasers, intense pulse light, and chemical peels. According to a review of randomized trials by Rajaratnam and colleagues, tretinoin and triple-combination creams are the most-effective treatments for melasma.[4] Taylor and colleagues reported a maximum efficacy of 26.1% for complete resolution,[6] but combination therapies are associated with more side effects (erythema, desquamation, burning, dryness, and pruritus), which are most common in patients receiving tretinoin and hydroquinone (80%), followed by tretinoin and fluocinolone acetonide.[6]

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As a physical blocker, zinc can provide broader protection against the sun than chemical blockers.[7] To the best of our knowledge, only a self-controlled study has been performed regarding the beneficial effects of topical zinc in melasma. That study reported that topical zinc sulfate (ZS) 10% plus sunscreen significantly reduced the severity of melasma.[8] According to the evidence, zinc has an important role in skin health, and topical zinc has various beneficial effects in the treatment of skin disorders,[7,9] but there are not enough data establishing that zinc could be effective in the treatment of melasma. The aim of our study was to investigate whether ZS is effective in reducing the severity of melasma by comparing it with HQ, a standard treatment for melasma.

Materials and Methods

Patients and settings

This randomized, double-blind, controlled trial was conducted on women with melasma referred to the outpatient dermatology clinic of Dr. Shariati Hospital, Isfahan (Iran) during 2010. We included all patients with any type of melasma (dermal, epidermal, or mixed) who had taken no medication within the 3 months before the study. Exclusion criteria were pregnancy, breast feeding, and using other medications, including hormones and antiepileptic agents. With α (type I error) = 0.05, study power = 0.8, and a minimum expected difference of 1 in melasma severity score, sample size was calculated as 39 patients in each group. The ethics committee of Islamic Azad University (Najaf Abad Branch) approved the study, and all patients signed informed consent before entering the clinical trial.

Intervention

Using a list generated using Random Allocation Software,[10] patients were randomly assigned to one of two groups of ZS 10% or HQ 4%. The ZS 10% solution contained ZS crystals dissolved in 90% water and 10% propylene glycol. The HQ solution contained 4% hydroquinone in 70% alcohol, 20% water, and 10% propylene glycol. Patients started using the solution for 2 hours once daily at night, gradually increasing its use to the complete night after 1 week. After washing the face in the morning, subjects covered their face with sunscreen (MY, SPF 60; Act Cosmetics Co., Tehran, Iran) and reapplied every 4 hours. This treatment with the solutions continued for 2 months, and patients were advised to use sunscreen for 3 months after the end of the treatment as well. Solutions were in the same boxes labeled A and B, and treatment status was not disclosed to investigators or patients throughout the study.

Assessments

We used transparent graph paper to precisely measure the affected area. A Wood lamp was used to distinguish epidermal, dermal, and mixed lesions. Patients were seen every 2 weeks, and melasma severity, using the Melasma Area and Severity Index (MASI), and drug reactions were evaluated. To calculate the MASI score, the sum of the severity grade for darkness (D) and homogeneity (H) was multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas. Total MASI score: (forehead 0.3 [D+H] $\times$ A) + (right malar 0.3 [D+H] $\times$ A) + (left malar 0.3 [D+H] $\times$ A) + (chin 0.1 [D+H] $\times$ A).[11] Patients were seen 3 months after the treatment finished, and the severity of their melasma was measured again.

Statistical analyses

Data were analyzed using SPSS for Windows version 16.0 (SPSS, Inc., Chicago, IL). Independent-sample *t*-tests and Mann–Whitney tests were used to compare parametric and nonparametric quantitative variables between groups respectively. Chi-square or Fisher exact tests were used to compare qualitative variables. Repeated-measure analysis was performed to evaluate trends in changes in MASI score during the study. Univariate and multivariate (linear regression analysis) analyses were conducted to find

TABLE 1. Participant and Disease Characteristics

Characteristic	*Zinc Sulfate,* n = *40*	*Hydroquinone,* n = *42*	p-*Value*
Age, mean ± SD	33.1 ± 9.1	35.2 ± 8.1	.27*
Type, *n* (%)			.43†
Epidermal	24 (60)	27 (64.2)	
Mixed	16 (40)	15 (35.7)	
Pattern, *n* (%)			.51†
Centrofacial	28 (70)	26 (61.9)	
Malar	10 (25)	15 (35.7)	
Mandibular	2 (5)	1 (2.3)	
Family history, *n* (%)	29 (72.5)	25 (59.5)	.16†
Onset at pregnancy, *n* (%)	25 (62.5)	21 (50)	.18†
Duration, months, mean ± SD	6.4 ± 5.1	6.0 ± 4.8	.73*
Sun exposure, h/d, mean ± SD	1.31 ± 0.57	1.10 ± 0.54	.09*
Baseline Melasma Area and Severity Index score, mean ± SD	6.2 ± 2.2	6.4 ± 1.6	.63*

SD, standard deviation.
*Independent sample t-test or Mann–Whitney test.
†Chi-square or Fisher exact test.

TABLE 2. Melasma Area and Severity Index Scores During the Trial According to Group

	Zinc Sulfate, n = *38*	*Hydroquinone,* n = *42*	
	Mean ± Standard Deviation		p-*Value**
Baseline	6.3 ± 2.1	6.4 ± 1.6	.93
Month 2	5.0 ± 1.9	3.6 ± 1.3	<.001
Month 5	5.1 ± 2.0	3.9 ± 1.4	.002
p-value†	<.001	<.001	
p-value‡	.02		

*Independent-sample *t*-test or Mann–Whitney test.
†Within- and ‡between-group repeated-measure test.

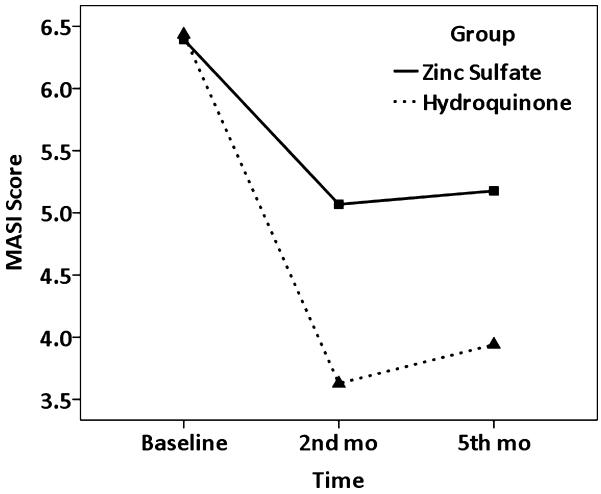

Figure 1. Changes in Melasma Area and Severity Index scores from baseline to month 5.

factors associated with treatment responses. $p < .05$ was set as the level of significance in all analyses.

Results

Demographic data and disease characteristics

Ninety-three patients were included into the trial. Eleven dropped out within 4 weeks after starting the study ($n = 9$ ZS, $n = 2$ HQ). Reasons for dropping out included drug side effects; distance from the treatment center and unwillingness to be followed. Data from 82 patients were used for the analyses. Patient data and disease characteristics are presented in Table 1. There were no significant differences between the two groups in demographic or disease characteristics.

Changes in MASI scores

MASI scores at baseline and at 2 and 5 months are presented in Table 2. Because two patients in the ZS group dropped out after the second month because of drug side effects, data from 38 patients were included in repeated-measure analysis from this

group. Analyses showed that MASI score fell significantly after the second (15.9 ± 29.5%) and fifth (18.6 ± 20.8%) months in the ZS group and in the HQ group (43.5 ± 15.5% and 38.3 ± 18.9%, respectively (within-group analysis, $p < .001$). MASI score fell more in the HQ than the ZS group (between-group analysis, $p = .02$; Figure 1).

Predictors of response

In univariate analyses, the response to treatment was better in patients with epidermal (32.8%) than mixed (22.5%) melasma ($p = .04$). Subgroup analysis showed that this difference occurred only in patients taking HQ (44.8% vs 26.5%, $p = .002$) and not in those taking ZS (18.8% vs 18.4%, $p = .95$). Regular use of sunscreen was associated with a greater decrease in MASI score ($r = 0.331$, $p = .003$). Other variables were not associated with response to treatment in univariate analyses. Linear regression analysis using a stepwise model controlling for all possible predictors showed that taking HQ ($\beta = 0.459$, $p < .001$) and regular use of sunscreen ($\beta = 0.315$, $p = .001$) were associated with a greater decrease in MASI score. Age, type of melasma, family history, sun exposure, melasma at pregnancy, and pattern of melasma were not significantly associated with a change in MASI score.

Drug side effects

Mild postinflammatory pigmentation occurred in two patients in the ZS group after the second month of therapy, but it resolved completely after treatment with topical tretinoin. The frequency of irritation was significantly higher in the HQ (30.9%)than the ZS (2.5%) group ($p < .001$). Recurrence rate was not different between the two groups (17.5% vs 23.8%, $p = .33$).

Discussion

Melasma is a skin hyperpigmentation disorder that does not resolve completely in most patients with current medications.[4,12] For the first controlled comparative trial, we considered zinc as a possible treatment for melasma because of its role in skin health. Zinc has antioxidative and anti-inflammatory properties, which may act as a regenerative substance in damaged skin. It can also protect skin from ultraviolet radiation, especially irritated skin, and so may prevent extra activity of melanocytes.[13,14] These mechanisms make zinc a potential therapeutic option for the treatment of melasma. Our data showed that topical zinc therapy is not highly effective for melasma. Although it reduced the MASI score after 2 months of treatment, and this effect was stable for at least 3 months after therapy, the MASI score fell more in the HQ group. These results show that ZS is not a suitable single treatment for melasma, and that it may be better to combine it with other topical agents such as HQ.

To the best of our knowledge, there is only one previous report regarding the therapeutic effects of zinc on melasma. In the study by Sharquie and colleagues, treatment with topical ZS 10% for 2 months resulted in 49.8% improvement in MASI score (from 9.45 to 4.70).[9] This greater percentage improvement in MASI score compared with our data may be as a result of several factors. Although the treatment plan was not clear in Sharquie study, zinc was applied twice daily in the previous report whereas we administered it once daily at night and thus did not take advantage of the sun-protective effects of zinc. Baseline severity of melasma was worse in the Sharquie and colleagues study than in ours (baseline MASI = 6.3), whereas in both studies, the final MASI score fell to approximately the same level. The previous study was an uncontrolled trial including 28 patients, half of whom did not complete the study, and it might be the case that mostly patients with a better response continued the follow-up. Regardless, both studies showed the beneficial effects of zinc in the treatment of melasma. Also, adjusting for confounding factors, multivariate analysis in our study supports that long-term use of sunscreen is important in the treatment of melasma.[15]

With regard to side effects, irritation occurred less commonly with ZS than HQ. Although, ZS caused

postinflammatory pigmentation in two cases in our study, this side effect was mild and resolved completely with topical tretinoin. Sharquie and colleagues did not report considerable side effects with topical zinc.[9] These results indicate that topical use of zinc is safe for long-term treatment of melasma, however, it is not known whether side effects are greater with combination therapies. Further trials are needed to evaluate the therapeutic effects and safety of zinc in combination with other agents for the treatment of melasma. Considering the role of zinc deficiency in skin health, oral zinc could be added to other topical therapies. This needs to be investigated.

There are some limitations to this study. We did not consider a sunscreen-only arm to evaluate the additional benefits of zinc over sunscreen. Also, considering the high recurrence rate of melasma, long-term follow-up was required to evaluate the effectiveness of topical zinc.

Conclusions

This study showed that topical zinc therapy has little beneficial effect in reducing the severity of melasma, and as a single agent, its effectiveness is much less than that of hydroquinone. It is possible that adding zinc to current topical treatments of melasma could increase the treatment response, which needs further trials regarding safety and efficacy.

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