Received: 4 September 2023 | Revised: 17 November 2023 | Accepted: 15 January 2024

DOI: 10.1002/hsr2.1930

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Successful treatment of solar lentigines by topical application of stabilized cysteamine: A vehicle-controlled, double-blind randomized study

Nasrin Saki[1,2] | Vahideh Modabber[1,2] | Hengameh Kasraei[3] | Behrooz Kasraee[4]

[1]Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Department of Dermatology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

[3]Eye Research Center, The Five Senses Health Institute, Rassoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran

[4]Swiss Vitiligo Center, Geneva, Switzerland

Correspondence
Hengameh Kasraei, Eye Research Center, The Five Senses Health Institute, Rassoul Akram Hospital, Bldg No 1, Eighth Floor, Niayesh Ave, Tehran, Iran.
Email: kasraeeh@yahoo.com

Funding information
Shiraz University of Medical Sciences, Grant/Award Number: IR.SUMS.MED.REC.1397.533

Abstract

Background: Solar lentigines are common hyperpigmented lesions typically appearing after 50 years of age and associated with negative psychological effects in affected individuals. Topical depigmenting products, such as hydroquinone and even the Kligman's formula, are usually ineffective for treating lentigines. Stabilized cysteamine has been recently shown to be as effective as the modified Kligman's formula for treating melasma. In this study, we evaluated the therapeutic effect of a stabilized cysteamine on solar lentigines.

Methods: A vehicle-controlled, double-blind, and randomized study was performed on 30 patients with solar lentigines. Stabilized cysteamine or vehicle control creams were applied on solar lentigines on the dorsum of the hands daily for 12 weeks. Clinical measurements with colorimetry and visual analog scale were performed at baseline, 4, 8, and 12 weeks.

Results: Statistically significant results were obtained in the cysteamine group versus the vehicle control group. Stabilized cysteamine provided a 40% reduction in colorimetric values ($p < 0.002$) versus a 2% reduction in the vehicle group ($p < 0.405$). Cysteamine also provided a 40% reduction in VAS ($p < 0.001$) versus a 2% reduction in the vehicle group ($p < 0.245$).

Conclusion: Significant improvement of solar lentigines was observed after 12 weeks of application of stabilized cysteamine by all evaluation methods. Stabilized cysteamine represents a highly effective topical treatment for solar lentigines and can be considered as one of the first topical therapies effective on this hyperpigmentary disorder.

KEYWORDS

hyperpigmentation, lentigines, randomized controlled trial, topical cysteamine

1 | INTRODUCTION

Solar lentigines are common and benign lesions of the skin resulting from life-long chronic exposure to sunlight.[1] Activating melanocytes in the skin's epidermis in response to UV radiation increases melanin production, causing the characteristic dark, well-defined spots. Histologically, solar lentigines exhibit features such as hyperplasia of melanocytes in the basal layer, increased melanin content, acanthosis, and elongation of rete ridges. While benign and harmless, these lesions are a cosmetic concern and often appear in sun-exposed areas. Protecting the skin from UV radiation prevents their formation and recurrence.[2] They typically appear after 50 years of age on sun-exposed areas, such as the face, neck, forearms, and dorsum of the hands as a result of skin photoaging; because of this, solar lentigines have a negative psychological impact causing a loss of self-esteem in affected individuals.[3,4] Solar lentigines present themselves in form of macules and hyperpigmented patches with defined margins ranging from a few millimeters to a few centimeters in size and are more common in light-skinned people. Solar lentigines result from a local proliferation of keratinocytes and basal melanocytes, causing a subsequent increase in melanization.[5]

Current treatments for solar lentigines often come with drawbacks, including temporary results, potential side effects, limited effectiveness for deep or stubborn spots, slow improvement, cost, accessibility issues, and the risk of depigmentation. Some treatments can increase sun sensitivity, necessitating additional sun protection. These limitations emphasize the need for better alternatives to treat solar lentigines effectively, rapidly, and with fewer side effects to this common cosmetic concern.[6] Conventional and effective methods for treating solar lentigines are quality-switched lasers, long pulse lasers, and intense pulsed light. Recently, short-pulsed, pigment-specific lasers became available. However, the high incidence of side effects, the most common being postinflammatory hyperpigmentation (PIH), represents a serious concern, especially in darker skin types.[7] Thus, the first line of treatment for hyperpigmentary disorders tends to be topical because of its simplicity, lower cost, less serious side effects, and does not require social eviction.

Topical treatments include depigmenting agents such as hydroquinone (HQ), tretinoin, adapalene, and retinoic acid. The mechanism of action of these agents relies on the inhibition of the melanin synthesis, in the case of HQ, or stimulation of epidermal cell turnover leading to dispersion of pigment and rapid loss of melanin via epidermopoiesis, in the case of retinoids.[8] The depigmenting activity of HQ was also improved by Dr. Kligman in 1975 by combining it with retinoic acid and a corticosteroid.[9] Despite the high depigmenting efficacy for treating hyperpigmentary disorders, such as melasma and postinflammatory hyperpigmentation, Kligman's formula is not effective on solar lentigines, as stated by Dr. Kligman himself.[9]

A topical depigmenting agent that has been receiving increasing attention from physicians in recent years is cysteamine. Cysteamine is the simplest aminothiol and endogenous antioxidant present in mammals. It derives from the Coenzyme A metabolism and has been demonstrated to be an efficacious depigmenting agent in several placebo-controlled clinical trials. It is compared to the most efficacious depigmenting agents, such as topical HQ and tranexamic acid mesotherapy.[10,11] Cysteamine effectively reduces melanin formation by inhibiting melanin synthesis at several levels, such as tyrosinase and peroxidase inhibition, preventing Fenton-type reactions by chelating iron and copper ions and increasing intracellular glutathione.[12] In addition, it has been shown that cysteamine might be more efficacious than the Kligman's formula for treating hyperpigmentary disorders.[11] To the best of our knowledge, cysteamine depigmenting efficacy was never tested against solar lentigines. Therefore, considering cysteamine's high depigmenting efficacy and safety, we first performed a study to evaluate the therapeutic effect of topical cysteamine on solar lentigines in a vehicle-controlled, double-blind, randomized study due to comparing visual analog scale, number of lesions, and mean Dermacatch score between two groups.

2 | MATERIALS AND METHODS

2.1 | Study design

A double-blind, randomized clinical trial was conducted on 30 patients suffering from solar lentigines. This research project was approved by the ethics committee of Shiraz University (ethical code and grant No IR.SUMS.MED.REC.1397.533).

Through calculation with Spower SCC software, with a significant difference of 1.5 and a standard deviation (SD) = 2, $\alpha = 0.05$, and $\beta = 0.2$, a sample of 30 patients was calculated. Thirty-three patients were included in the study and randomly divided into two groups (cysteamine or vehicle group).

Inclusion criteria were as follows: men and women between 18 and 90 years old with dermoscopically confirmed solar lentigines on the dorsal side of the hand. Patients treated with other topical medications or other types of physical treatments within 1 month before the study, as well as breastfeeding and pregnant mothers, were excluded from the study. First, the total sample size was divided into four blocks. Then, each block was divided into intervention or nonintervention groups based on the table of random numbers. In this way, it was impossible to guess how the patients were placed in the intervention and nonintervention groups. The trial was double-blind, and the patients and the people who administered the drug to the patient and recorded the results did not know the type of drug or placebo after data analyzing block codes revealed by the supervisor. The dermatologist obtained informed consent and explained the research condition to the patients. They were taking photographs, and the dermatologist explained the follow-up duration. A visit to a dermatologist was made free of charge for patients to facilitate the follow-up of patients. Creams were provided to patients for free. The thirty patients with lentigines on the dorsal side of their hands were randomly divided into two groups and received cysteamine cream (Cyspera®, Scientis SA) or vehicle control cream. Each patient was given a unique code, and all patient information was collected anonymously.

3 | MODE OF APPLICATION

Study participants were instructed to apply the products as a thin layer on unwashed skin. The exposure time was set to be 15 min, after which the products were rinsed off using a gentle cleanser. As a third step, patients were advised to use a moisturizing cream to prevent skin dryness and avoid any adverse events. All the ingredients in both groups of cream were the same except cysteamine, which was used only in the case group. 3% Urea cream was used as a moisturizer in both groups. Patients were instructed to apply sunscreen of at least sun protection factor (SPF) 50, to be reapplied every 3 h during exposure to sunlight.

3.1 | Clinical endpoints

Visual and instrumental assessments were performed at baseline, week 4, 8, and 12. A follow-up of 12 weeks was chosen after reviewing the literature compared with the other types of treatments. In each visit, lesions were counted, and skin colorimetry measurements were performed using Dermacatch (Delfin Technologies Ltd.). The mean Dermacatch score (MDS) was calculated by the investigators as follows: in lentigines with a maximum diameter of 5 mm, the melanin index was measured at the center of the lesion, and in lentigines with a diameter higher than 5 mm, the lentigo was divided into four quadrants and the average melanin index of these four quadrants was considered. A visual analog scale (VAS) was used to subjectively evaluate patients' feedback on the evolution of the lesions. High-resolution images of the dorsum of the hands were acquired by a camera (Canon DS126371).

We conducted the Mann–Whitney *U* test, independent samples *T* test, Wilcoxon signed-rank test, and paired sample *T* test to analyze our data. The significance level for our study was set at 0.05.

4 | RESULTS

Thirty-three patients were included in the study and randomly divided into two groups (cysteamine or vehicle group). The mean age of the study participants was 49.47 ± 9.69 (SD). Both group's gender was the same as each other four males and 11 females. The mean ± SD of patients in the vehicle and cysteamine groups was 49.3 ± 11.6 and 49.6 ± 7.7, respectively. The lesions on each hand of each patient were separately examined and evaluated at follow-ups. In each group, three patients had solar lentigines on one hand only. Finally, thirty patients completed the study (Figure 1). Of these, eight were males and 22 females; the two genders were equally distributed among the two study groups. Only 30% of patients routinely used sunscreen on the dorsum of their hands, and 90% of patients had a positive family history of solar lentigines in their first-degree relatives. 40% of patients had a history of using lentigines-relieving products in the past. Previous use of antilentigines products was

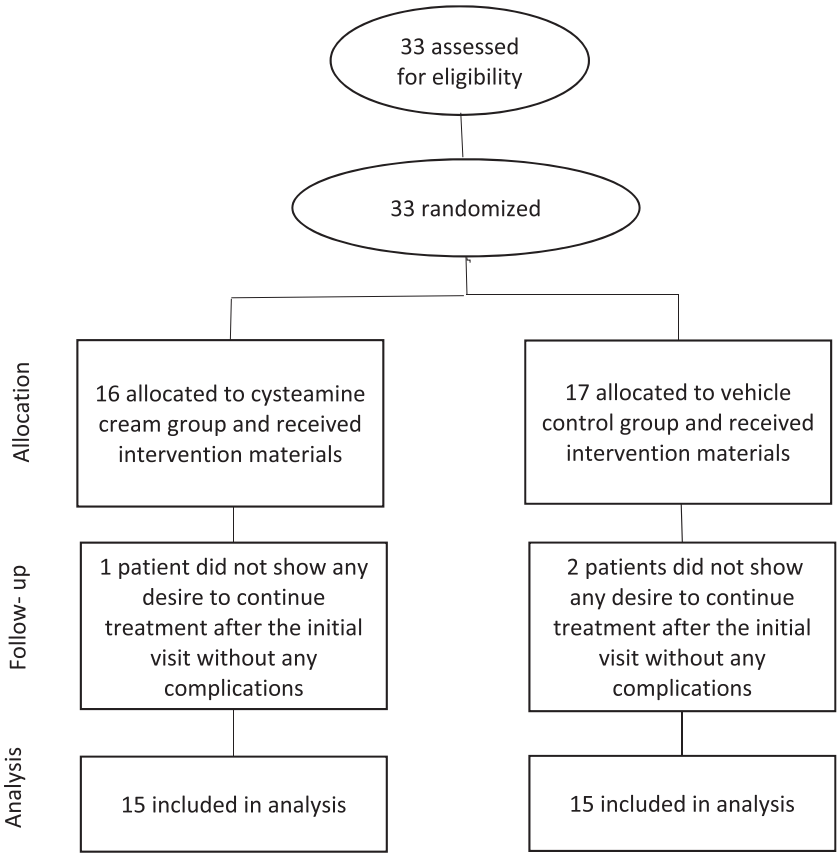

FIGURE 1 Flow diagram.

TABLE 1 Results on VAS, number of lesions and MDS for each group at each visit.

	Vehicle control ($n = 27$)	Cysteamine ($n = 27$)	p Value
Baseline			
VAS [mean rank (min, max)][a]	21.87 (5, 10)	33.13 (4, 10)	0.008
No [mean rank (min, max)][a]	26.67 (1, 14)	28.33 (1, 16)	0.696
MDS, mean (SD)[b]	397.11 (126.00)	481.29 (145.98)	0.027
4 weeks			
VAS [mean rank (min, max)][a]	26.96 (5, 10)	28.04 (3, 9)	0.798
No [mean rank (min, max)][a]	27.28 (1, 14)	27.72 (1, 16)	0.917
MDS, mean (SD)[b]	380.81 (126.80)	414.00 (154.05)	0.391
8 weeks			
VAS [mean rank (min, max)][a]	33.74 (4.5, 10)	21.26 (2, 8.5)	0.003
No [mean rank (min, max)][a]	28.00 (1, 13)	27.00 (0, 15)	0.814
MDS, mean (SD)[b]	374.74 (133.37)	349.96 (143.39)	0.514
12 weeks			
VAS [mean rank (min, max)][a]	37.02 (4.5, 10)	17.98 (2, 8.5)	<0.001
No [mean rank (min, max)][a]	28.41 (1, 13)	26.59 (0, 15)	0.670
MDS, mean (SD)[b]	387.48 (126.72)	294.07 (140.55)	0.013

Abbreviations: MDS, mean dermacatch score; No, number of lesions; VAS, visual analogue scale.

[a]Mann–Whitney U test, $p < 0.05$ is significant.

[b]Independent-samples T test, $p < 0.05$ is significant.

compared between the two groups, and no statistically significant difference between the two groups was found ($p = 0.4$). Patients were prohibited from using products other than those prescribed by the researcher during the study.

At the beginning of the study, the cysteamine group was evaluated with a statistically significant higher VAS ($p = 0.008$) and MDS ($p = 0.027$) than a vehicle control group. At week 4 no statistically significant difference was observed between the two groups in any of the assessments. At week 8, VAS was significantly lower in cysteamine group compared to the vehicle group ($p = 0.003$). At week 12, statistically significant differences in VAS ($p < 0.001$) and MDS ($p = 0.013$) were observed between the two groups (Table 1).

At week 12, statistically significant differences were observed when comparing the efficacy of cysteamine versus one of the vehicle control on all parameters. The results and statistical analysis are given in the table below (Table 2 and Figure 2).

At week 12, significant improvements in solar lentigines were also observed from the high-resolution clinical images (Figure 3).

5 | DISCUSSION

This study aimed at investigating topical cysteamine's efficacy in treating solar lentigines. Generally, these benign hyperpigmented lesions appear as we age; because of this, they are often referred to as "age spots" or "senile lentigines." The treatment of such lesions is challenging because of the lack of efficacious topical treatments and their high recurrence rate after laser therapy. On the other hand, the recurrent nature of solar lentigos makes it even more apparent that a suitable topical treatment must be safe enough for long-term use.

The most effective treatments are physical procedures, such as lasers, chemical peels, and cryotherapy. The latter is used in treating single solar lentigines lesions; however, adverse events such as pain and hypopigmentation of the skin after treatment cannot be excluded.[13,14] Short-pulsed, pigment-specific lasers are widely used in clinics; however, their effectiveness is highly dependent on individual responses, which may vary widely.[15]

TABLE 2 Results at 12 weeks versus baseline for each treatment group.

	Statistical test	Group	Baseline (mean ± SD)	12 weeks (mean ± SD)	p Value[a]
VAS	Wilcoxon signed-rank test	Vehicle control	7.33 ± 0.25	7.46 ± 0.25	0.154
		Cysteamine	8.27 ± 0.30	5.09 ± 0.35	<0.001
Number of lesions	Wilcoxon signed-rank test	Vehicle control	6.25 ± 0.79	6.37 ± 0.78	0.405
		Cysteamine	6.66 ± 0.84	5.88 ± 0.78	0.002
MDS	Paired sample T test	Vehicle control	397.11 ± 24.24	387.41 ± 24.38	0.245
		Cysteamine	481.29 ± 28.09	294.07 ± 27.05	<0.001

[a]p Value < 0.05 is considered significant.

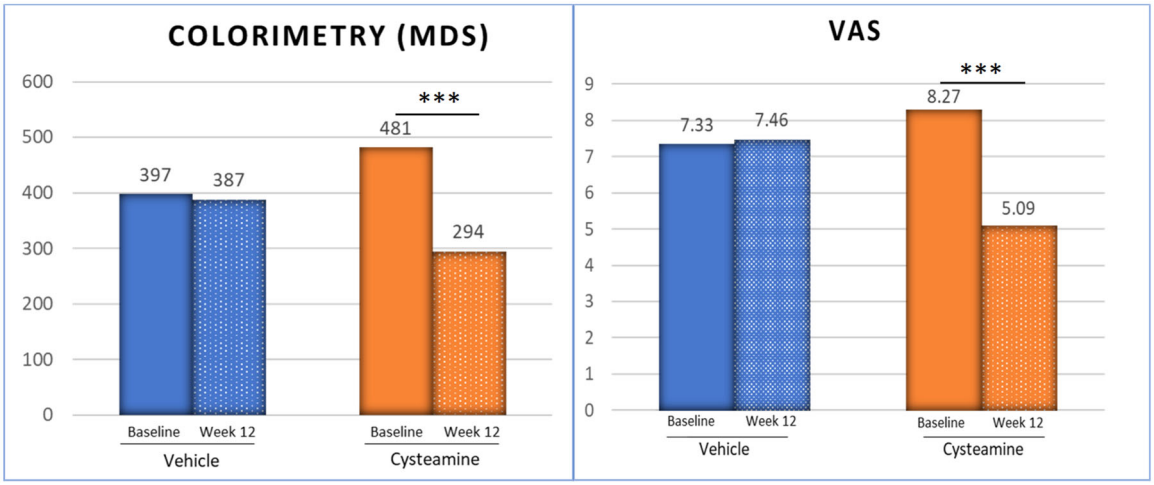

FIGURE 2 Baseline and week 12 results from daily short-contact topical application of cysteamine formulation on visual analog scale (VAS) and mean Dermacatch score (MDS).

Topical products, including the Kligman's formula, are usually ineffective in removing solar lentigines.[9]

Cryosurgery methods are used to treat single solar lentigo lesions, including complications such as pain and hypopigmentation of the skin after treatment.[14] Laser can also be used to treat these lesions, but the response of different patients to this treatment can be very different, which is considered a weakness in the use of laser.[15] Raziee et al. have compared the use of cryotherapy with the use of Trichloroacetic acid and have shown that the effectiveness of cryotherapy was higher than that of Trichloroacetic acid, and in both treatments, side effects such as postinflammatory hyperpigmentation was observed.[13] Other available treatments used as topical creams are used in two general categories of retinoids and bleaching agents or combination. Due to the side effects of each of these methods and their relative effectiveness, various studies have been conducted to compare their effectiveness.

Hydroquinone is a bleaching compound; despite its cytotoxicity, it is still used as a single depigmentation agent and in combination with other treatments in patients with solar lentigines.[16,17] Tadokovo et al. have shown that the use of orchid plant extract had an equal effect on that of VitC-containing compounds on reducing lesions' size and color intensity and increasing skin radiance.[18] Yamada et al. also investigated the effect of Phalaenopsis orchid extract in vitro and showed that this extract inhibits stem cell differentiation of melanocytes by suppressing WNT1 expression.[19]

Cysteamine is a depigmenting molecule that has gained more and more attention in recent years. Cysteamine is an endogenous molecule resulting from the natural degradation of L-cysteine during the co-enzyme A metabolism. It is an antioxidant having a long history of safety for human use.[20,21] Human studies have shown cysteamine exerts antimutagenic, anticarcinogenic, and antimelanoma activities. In 1966, Dr. Chavin found cysteamine to be a depigmenting agent after injecting cysteamine hydrochloride into the skin of a black goldfish. It was later demonstrated that cysteamine inhibits melanin synthesis at different levels of the melanogenesis pathway. Cysteamine reduces the activity of melanogenic enzymes tyrosinase and peroxidase; it chelates iron and copper, preventing tyrosine conversion into dopaquinone.[12] Cysteamine was proven to be as effective as HQ and tranexamic acid mesotherapy for treating melasma in two independent clinical studies.[11,22] In a more recent double-blind clinical trial, it was shown that cysteamine combined with isobionic-amide provides the same efficacy and onset of action as the Kligman's formula for treating melasma (article in press). Some other studies suggest the efficacy of cysteamine formulations compared to Kligman's formula for treating hyperpigmentary disorders.[11,23] Our study represents the first clinical evidence of the efficacy of topical cysteamine on a group of patients with solar lentigines.

The results of our study showed, for the first time, that 12 weeks of daily application of cysteamine cream resulted in a statistically significant improvement in MDS, and VAS as well as a reduction of the number of lesions. In contrast, the vehicle control group did not show any significant improvements. Visual assessment of the high-resolution images further supported the quantitative data. Thus, topical cysteamine proved to be an effective topical treatment for solar lentigines, providing a visible reduction of pigmentation and the number of lentigines on the dorsum of the hands.

However, our study has some limitations. Because of limited resources, having cysteamine and vehicle control in the same patient was impossible. Paying attention to this issue can lower the bias of the study due to better matching in different aspects. In addition, although a structural analysis of lentigines through skin biopsies could have added more information on the mode of action of cysteamine leading to the observed clinical effect, it is not logical to do, which is an invasive method. In future studies, cysteamine should be evaluated on a larger scale and multicenter trial, and its efficacy should be compared with other depigmenting modalities. Paying attention to the long-term efficacy of cysteamine, which is also

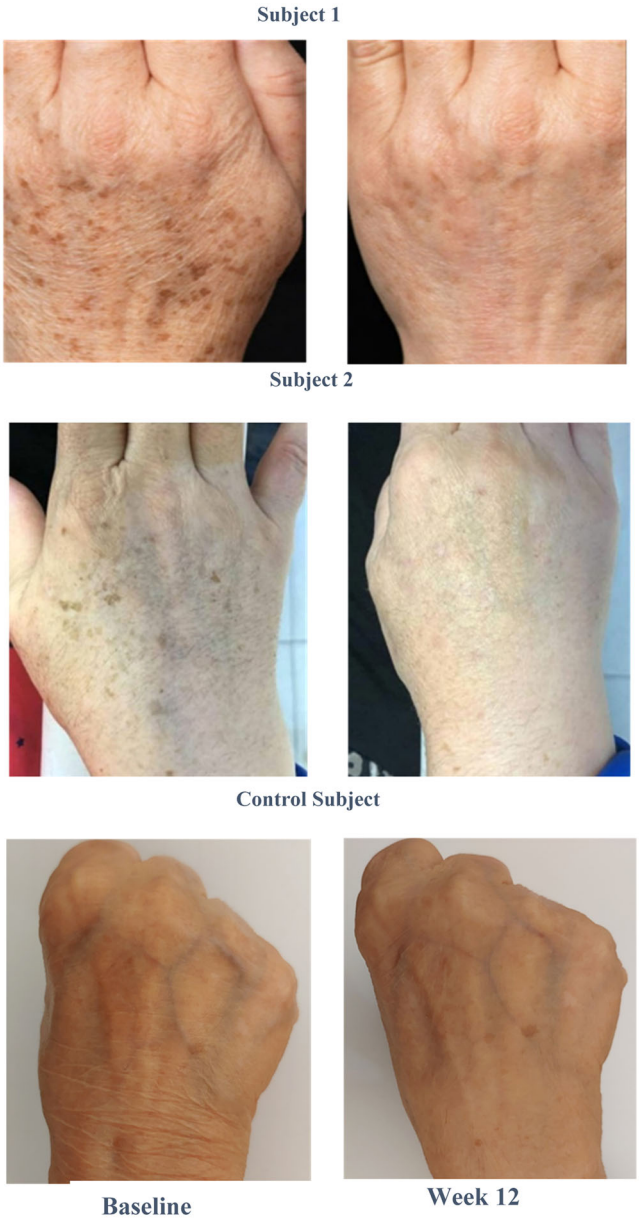

FIGURE 3 Baseline and week 12 results from daily short-short contact topical application of cysteamine formulation and control subject.

suitable for the long-term maintenance treatment of solar lentigines after laser therapy, is recommended in future studies that reduce the need for repeated laser treatments. This possibility needs to be addressed in future studies.

AUTHOR CONTRIBUTIONS

Nasrin Saki: Conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; validation; visualization; writing—review and editing. **Vahideh Modabber**: Data curation; project administration; writing—review and editing. **Hengameh Kasraei**: Formal analysis; writing—original draft. **Behrooz Kasraee**: Conceptualization; methodology; project administration; resources; writing—review and editing.

ACKNOWLEDGMENTS

The present article was extracted from the thesis written by Vahideh Modabber, which was financially supported by Shiraz University of Medical Sciences (ethical code and grant No IR.SUMS.MED.REC.1397.533). The researchers would like to thank the participants sincerely; without their collaboration, producing this article would be impossible.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

TRANSPARENCY STATEMENT

The lead author Hengameh Kasraei affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Hengameh Kasraei http://orcid.org/0000-0002-3989-4430

REFERENCES

1. Ortonne JP. Pigmentary changes of the ageing skin. *Br J Dermatol*. 1990;122(suppl 35):21-28.
2. Nakamura M, Morita A, Seité S, Haarmann-Stemmann T, Grether-Beck S, Krutmann J. Environment-induced lentigines: formation of solar lentigines beyond ultraviolet radiation. *Exp Dermatol*. 2015;24(6):407-411.
3. Bastiaens M, Hoefnagel J, Westendorp R, Vermeer BJ, Bouwes Bavinck JN. Solar lentigines are strongly related to sun exposure in contrast to ephelides. *Pigment Cell Res*. 2004;17(3):225-229.
4. Taylor A, Pawaskar M, Taylor SL, Balkrishnan R, Feldman SR. Prevalence of pigmentary disorders and their impact on quality of life: a prospective cohort study. *J Cosmet Dermatol*. 2008;7(3):164-168.
5. Plensdorf S, Martinez J. Common pigmentation disorders. *Am Fam Physician*. 2009;79(2):109-116.
6. Cantisani C, Cantoresi F, Mercuri SR, et al. Efficacy of imiquimod 3.75% cream for the treatment of solar lentigo. *Dermatol Ther*. 2020;33:1-2.
7. Negishi K, Akita H, Matsunaga Y. Prospective study of removing solar lentigines in Asians using a novel dual-wavelength and dual-pulse width picosecond laser. *Lasers Surg Med*. 2018;50(8):851-858.
8. Geria AN, Lawson CN, Halder RM. Topical retinoids for pigmented skin. *J Drugs Dermatol*. 2011;10(5):483-489.
9. Kligman AM. A new formula for depigmenting human skin. *Arch Dermatol*. 1975;111(1):40-48.
10. Besouw M, Masereeuw R, van den Heuvel L, Levtchenko E. Cysteamine: an old drug with new potential. *Drug Discovery Today*. 2013;18(15-16):785-792.

11. Karrabi M, David J, Sahebkar M. Clinical evaluation of efficacy, safety and tolerability of cysteamine 5% cream in comparison with modified Kligman's formula in subjects with epidermal melasma: a randomized, double-blind clinical trial study. *Skin Res Technol*. 2021;27(1):24-31.
12. Desai S, Hartman C, Grimes P, Shah S. Topical stabilized cysteamine as a new treatment for hyperpigmentation disorders: melasma, post-inflammatory hyperpigmentation, and lentigines. *J Drugs Dermatol*. 2021;20(12):1276-1279.
13. Raziee M, Balighi K, Shabanzadeh-Dehkordi H, Robati R. Efficacy and safety of cryotherapy vs. trichloroacetic acid in the treatment of solar lentigo. *J Eur Acad Dermatol Venereol*. 2008;22(3):316-319.
14. Sezer E, Erbil H, Kurumlu Z, Taştan HB, Etikan I. A comparative study of focal medium-depth chemical peel versus cryosurgery for the treatment of solar lentigo. *Eur J Dermatol*. 2007;17(1):26-29.
15. Bukvić Mokos Z, Lipozencić J, Pasić A, Fattorini I. Laser therapy for solar lentigines: review of the literature and case report. *Acta Dermatovenerol Croat*. 2006;14(2):81-85.
16. Hexsel D, Hexsel C, Porto MD, Siega C. Triple combination as adjuvant to cryotherapy in the treatment of solar lentigines: investigator-blinded, randomized clinical trial. *J Eur Acad Dermatol Venereol*. 2015;29(1):128-133.
17. Mansouri P, Farshi S, Hashemi Z, Kasraee B. Evaluation of the efficacy of cysteamine 5% cream in the treatment of epidermal melasma: a randomized double-blind placebo-controlled trial. *Br J Dermatol*. 2015;173(1):209-217.
18. Tadokoro T, Bonté F, Archambault JC, et al. Whitening efficacy of plant extracts including orchid extracts on Japanese female skin with melasma and lentigo senilis. *J Dermatol*. 2010;37(6):522-530.
19. Yamada T, Hasegawa S, Inoue Y, et al. Inhibitory effect of phalaenopsis orchid extract on WNT1-induced immature melanocyte precursor differentiation in a novel in vitro solar lentigo model. *Biosci Biotechnol Biochem*. 2016;80(7):1321-1326.
20. Ariceta G, Giordano V, Santos F. Effects of long-term cysteamine treatment in patients with cystinosis. *Pediatr Nephrol*. 2019;34(4):571-578.
21. Liang H, Labbé A, Baudouin C, Plisson C, Giordano V. Long-term follow-up of cystinosis patients treated with 0.55% cysteamine hydrochloride. *Br J Ophthalmol*. 2021;105(5):608-613.
22. Nguyen J, Remyn L, Chung IY, et al. Evaluation of the efficacy of cysteamine cream compared to hydroquinone in the treatment of melasma: a randomised, double-blinded trial. *Australas J Dermatol*. 2021;62(1):e41-e46.
23. Kasraee B, Mansouri P, Farshi S. Significant therapeutic response to cysteamine cream in a melasma patient resistant to Kligman's formula. *J Cosmet Dermatol*. 2019;18(1):293-295.

How to cite this article: Saki N, Modabber V, Kasraei H, Kasraee B. Successful treatment of solar lentigines by topical application of stabilized cysteamine: a vehicle-controlled, double-blind randomized study. *Health Sci Rep*. 2024;7:e1930. doi:10.1002/hsr2.1930