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TO ASSES EFFICACY AND SAFETY OF TOPICAL 5% CYSTEAMINE CREAM VS. KOJIC ACID 3% CREAM IN TREATMENT OF FACIAL MELASMA IN FEMALES: A COMPARATIVE STUDY

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ABSTRACT

Background: To assess the efficacy and safety of topical 5% cysteamine versus kojic acid 3% creamin the treatment of facial melasma in women. Topical 5% cysteamine is an antioxidant and tyrosinase inhibitor that has been shown to be effective in the treatment of melasma. However, there are very lessstudies comparing the performance of topical cysteamine to kojic for facial melasma.

Materials and Methods: A quasi-randomized, multicenter,clinical trial was conducted on 40 women with facial melasma who were randomly allocated to nightly application of 5% cysteamine (CYS) or 3% kojic acid on hyperpigmented areas of melasma for 6 months.Both groups were prescribed sunscreen (SPF 50). Subjects were assessed at the visit and after 3months, and 6 months treatment for mMASI score and MELASQoL.The Global Improvement Scale was also used to assess the difference in the appearance of the skin through standardized photographs.

Results: The mean reduction of the mMASI scores was 24% for CYS and 21% for KJ (P = 0.015) at 3 months, and 38% for CYS and 33% for KJ(P = 0.017) at 6 months. The photographic evaluation revealed up to 64% improvement for both groups, without statistically significant difference between them (P = 0.087). The MELASQoL score showed a progressive decrease for both groups over time, with the greater reduction with CYS. No severe adverse effects were identified in either group. Erythema and burning were the two most important local adverse effects with cysteamine, although their frequency did not differ statistically between groups (P > 0.170).

Conclusion: Cysteamine proved to be safer, better and well-tolerated and effective, compared to kojic acid in decreasing mMASI, MELASQoL and GAISin the treatment of melasma.

Keywords: cysteamine, efficacy, kojic acid, melasma, and safety.

INTRODUCTION

Melasma is a common macular hyperpigmentary disorder that affects photoexposed areas, especially in women of childbearing age group.[1]Melasma is nearly treatment resistanct with frequent relapses, despite the use of broad-spectrum sunscreen and topical bleaching agents,among others.[2-4] The quality of life in patients is severely impaired because of the chronicity of the disease and tendency to recur despite measure, specially in women where more importance is given to appearance related attributes.[5,6]The majority of the effective depigmenting agents are tyrosinase inhibitors, of which hydroquinone is the most-studied drug.[3,4] Kojic acid (KA) is hydrophilic fungal derivative that inhibits tyrosinase, by chelating copper at the active site of the enzyme. It is used in a concentration of 1%–4%, and has come

up as a safe and effective alternative, used both alone and in combinations. Various studies have been done to evaluate its role in melasma and these have shown mixed results.[7,8] L-cysteamine (b-mercaptoethylamine hydrochloride) is an aminothiol compound with antioxidant and depigmenting properties.[9] It can be found naturally in mammals as an intracellular degradation product of L-cysteine.[10] The exact mechanism by which cysteamine inhibits melanogenesis is not fully understood, but it increases intracellular glutathione, which shifts theeumelanin to pheomelanin synthesis. Cysteamine is available worldwide as oral capsules (bitartrate) and ophthalmic solution (hydrochloride) for the treatment of cystinosis. A recent change in the formulation of cysteamine led to the reduction in the sulfur odor and skin irritability, allowing its use as a cream that has proven to be effective in the topical treatment of pigmentary disorders.[11-13] However, to date no study has compared this formulation of topical cysteamine to 4% hydroquinone in the treatment of melasma.

MATERIALS AND METHODS

In this study, we aimed to assess the efficacy and safety of topical 5% cysteamine versus 3% kojic acidin the treatment of facial melasma in women. We performed a quasi-randomized, multicenter, parallel, clinical trial. Forty women with facial melasma. Patients were submitted to a nightly application of 5% cysteamine (CYSgroup) or 3% kojic acid (KJ group) over their lesions for a total duration of 6 months. The diagnosis of melasma was established clinically. The inclusion criteria were women with facial melasma, with skin phototype II to V, and aged between 30 and 55 years old. We did not include women who were pregnant, had undergone menopause, had other facial dermatoses, or were receiving bleaching treatments for melasma other than sunscreen for at least one month(washout). The eligible participants were allocated to the groups in a sequential (randomized) order The study was performed between September 2023 and February 2024. The participants in the CYS-group were instructed to apply 5% cysteamine gel-cream on their facial lesions at night, followed by facial washing. The participants were asked to leave the cream for15 minutes in the first night and progressively increase the time up to 2 hours, if there was no skin irritation, in the subsequent nights. The participants in the KJ group wereto apply topical 3% kojic acid cream on their facial lesions at bedtime; the product should remain on the face overnight, with morning washing.

Both groups were required to use a similar sunscreen (SPF 50;) with thrice reapplication in a day.

Subjects were also assessed at the inclusion and after 3 months and 6 months of treatment by modifiedMelasma Area and Severity Index (mMASI),Melasma Quality of Life Scale (MELASQoL).[14,15] The Global Aesthetic Improvement Scale (GAIS) was used to assess the difference in the appearance of the skin through photographs.[16]

Table 1: Demographic data and baseline

	CYS(cysteamine)	KJ,(kojic acid)	Total
Age(mean)	36	38	38
Skin type(II-III)	5	13	18(45%)
Skin type(IV-V)	15	7	22(55%)
Family occurance	14	15	29(73%)
Duration	12	14	13
Daily sun exposure (min)	10	15	12
mMASI	9	6	7
MELASQoL	55	45	50

The compliance of participants was assessed at 3 months and 6 months by inquiring about the duration of cysteamine tolerability(15 minutes to 2 hours), the number of days per week for which the treatment was applied, and the frequency of sunscreen use.

The adverse effects, such as facial erythema,scaling, and burning sensation, were assessed at 3 months and 6 months.The mMASI is the most commonly used parameter for assessing facial melasma severity. It is composed of standardized scores of area and the intensity of the pigmentation in facial units, assessed at the clinical examination. 17 MELASQoL is an important questionare for evaluating quality of life related to melasma. It is comprised of 10 self-response items regarding feelings associated with the melasma, over the previous week. 18,19 The correlation between the rate of mMASI decrease and the skin contact time with cysteamine was assessed by Spearman's rank correlation coefficient (rho). Data were analyzed using the software IBM SPSS 25.

RESULTS

The groups did not differ in their main baseline data (i.e., demographics, mMASI, MELASQoL; Table 1). There were no drop outs. All groups exhibited a reduction in mMASI and MELASQoL scores (Table 2), as well as up to 64% photographic improvement (Fig. 2). Notwithstanding, the CYS -group showed earlyimprovement in mMASI scores and a final superior MELASQoL reduction, compared to KJ-group.

Table 2: Study Outcome INterms of mMASI, m MELASQOL and GAIS

	CYS	KJ	P value
mMASI (0)	10	5	0.14
mMASI (3)	7	3	0.02
mMASI (6)	5	2	0.02
MELASQoL (0)	50	55	0.07
MELASQoL (3)	38	46	0.131
MELASQoL (6)	29	40	0.081
GAIS UNALTERED	3	6	
GAIS IMPROVED	14	12	
GAIS V. IMPROVED	2	1	
GAIS EXCELLENT	1	0	

At 3 months s, the mean (CI 95%) reductions of the mMASI scores were 24% for CYS and 21% for KJ (P = 0.015). At 6 months, these values were 38%for CYS and 33% for KJ(P = 0.017). There were no differences between groups regarding the adherence to sunscreen and the topical treatments (Table 2).Most participants tolerated up to 1 hour of cysteamine on their facial lesions at 6 months. Despite recommendation to use cysteamine for up to 2 hours, two participants reported overnight facial contact time with the cysteamine cream at 6 months.The odor from the cysteamine was considered by the participants to be tolerable and completely subsided after facial washing.

Table 3: Adherence to treatment protocol and tolerability of cysteamine

	CYS	KJ	P value
Sunscreen compliance at 3months	3.1	2.5	0.769
Sunscreen compliance at 6 months	3.1	2.8	0.689
Cysteamine contact time < 30 min	2	-	
Cysteamine contact time30 min- 1 hour	8	-	
Cysteamine contact time >1 hour	10	-	

There were no severe adverse effects related to the treatments (Table 4).Erythema and burningsensation were the symptoms reported in up to 20% of the CYS-group. Tolerability regarding erythema, desquamation, andburning did not differ between the groups (P > 0.17). [Table 3]

DISCUSSION

This trial confirmed the efficacy and acceptability of the novel topical cysteamine formulation for the treatment of facial melasma and compared its aspects to those of topical kojic acid. The low attrition rate reinforces the tolerability of the treatments and the comparability between the groups. The women who participated in this study were representative of a North Indian middle age female population. Despite the adequate balance between the groups, the predominance of darker phototypes, more frequently reported family history of melasma, long disease duration, and longer outdoor hours were issues that may have promoted irregular responses to the treatments.[22]The mMASI scores progressively reduced over time for both groups, despite the CYS group perceiving faster depigmentation.A longer follow-up to assess the maximum outcomes and therate of relapse after the suspension of the treatments should be evaluated through specific designs. The results of other trials revealed a mean 38–58% decrease in mMASI scores promoted by topical cysteamine after 6 months, which is consistent with our results.[12,13,23]

Itching and burning were reported as the most common adverse effects in up to 43% of patients in other trials, and erythema was considered to be severe in up to 18–20% of patients.[11,12,23] As the tolerability of cysteamine is time-dependent, these symptoms should drive the progressive duration of long-term efficacy of cysteamine as well as its use as a maintenance treatment after other potent depigmenting agents (e.g., hydroquinone), laser or oral tranexamic acid are needed in order to position it among the existing strategies for the management of melasma.[15,28]

CONCLUSION

In conclusion, topical 5% cysteamine proved to be safe, well-tolerated, and moreeffectiveas compared to 3% kojic acid, in decreasing mMASI and MELASQoL in the treatment of melasma after 6 months.

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