Section: Dermatology

Original Research Article

EVALUATION OF THE EFFICACY OF 5% CYSTEAMINE CREAM COMPARED TO TRIPLE COMBINATION CREAM IN THE TREATMENT OF MELASMA. A DOUBLE BLINDED RANDOMIZED CONTROL TRIAL

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ABSTRACT

Background: Melasma is a prevalent acquired condition characterised by facial hyperpigmentation, especially among women with darker skin phototypes. The fluocinolone–hydroquinone–tretinoin triple-combination (TC) cream is still the best treatment, but worries about irritation, rebound pigmentation, and long-term safety have led to the search for safer options like cysteamine, a natural antioxidant that is very effective at removing pigment. **Objective:** To compare the efficacy, safety, and patient satisfaction of 5% cysteamine cream with the conventional triple-combination cream in the treatment of facial melasma. **Materials and Methods:** This prospective, double-blinded randomised controlled trial was executed at a tertiary care facility in Tamil Nadu, India, from January to June 2025. Fifty adults with clinically diagnosed facial melasma were randomised into two equal groups to receive either 5% cysteamine cream or triple-combination cream once daily for 12 weeks, along with photoprotection. The modified Melasma Area and Severity Index (mMASI) and Melasma Quality of Life Scale (MELASQOL) were checked at the beginning, week 4, week 8, and week 12. **Result:** Both groups had lower mMASI scores than they did at the start of the study, but the cysteamine group saw more improvement starting in week 8 (mean mMASI at week 12: 5.19 ± 1.98 vs. 6.49 ± 2.16; p = 0.01). Both groups' MELASQOL scores went up a lot, but the cysteamine group showed a bigger improvement at week 12 (p = 0.028). There were more adverse events with the triple-combination cream (56%) than with the cysteamine (24%), but all of them were mild and went away quickly. **Conclusion:** Cysteamine 5% cream showed better effectiveness than the triple-combination cream, and it was much safer and easier to use. It is a promising alternative to hydroquinone for treating and keeping facial melasma under control over the long term, especially for people with darker skin types.

INTRODUCTION

Melasma is a condition that people get that causes dark spots on their faces. It mostly affects women with darker skin types. It appears as brown to gray-brown spots and patches that aren't even on parts of the body that get a lot of sun. Its complicated pathophysiology includes genetic predisposition, exposure to UV and visible light, hormonal impacts, and changes in the dermal microvasculature, all of which make it more likely to come back and last a long time. The disorder has a big effect on people's mental health because it changes how they look and how they feel about themselves.[1] The fluocinolone–hydroquinone–tretinoin triple-combination (TC) cream remains the gold-standard topical therapy for melasma, offering synergistic inhibition of melanogenesis and epidermal turnover acceleration. Long-term studies have demonstrated efficacy up to 80 % of patients achieving near-complete clearance of lesions over 12 months of period.[2] But hydroquinone-based treatments have problems like irritation, rebound hyperpigmentation, exogenous ochronosis, and the possibility of causing mutations, which shows that we need safer options.[3]

Cysteamine, an endogenous aminothiol and natural antioxidant resulting from coenzyme A metabolism, has recently been identified as a potential depigmenting agent. Its mechanism involves the inhibition of tyrosinase, peroxidase, and the

conversion of dopaquinone, as well as antioxidant effects that alleviate oxidative stress in melanocytes.[4] In several randomised controlled trials, 5% cysteamine cream exhibited substantial enhancement in the Melasma Area and Severity Index (MASI) and colorimetric assessments relative to placebo, demonstrating comparable efficacy to 4% hydroquinone, while offering superior tolerability and patient satisfaction.[5-7] Recent head-to-head and split-face randomized studies have reported that cysteamine, whether alone or combined with ectoine, achieves pigmentation reduction and quality-of-life improvement comparable to hydroquinone-based formulations, without significant differences in efficacy or adverse events.[8,9]

Although there is growing evidence of cysteamine's effectiveness and safety, there are still not many direct comparisons between cysteamine and the triple-combination cream, which is the standard treatment for melasma on the skin. This double-blind, randomised controlled trial seeks to assess and compare the efficacy, safety, and patient satisfaction outcomes of 5% cysteamine cream versus the triple-combination cream in individuals with facial melasma.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, double-blinded, randomised controlled trial conducted in the Department of Dermatology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre, Tamil Nadu, India. The study period was from January 2025 to June 2025. The trial compared the efficacy and safety of 5 % cysteamine cream with a triple-combination cream containing 4 % hydroquinone, 0.05 % tretinoin, and 0.01 % fluocinolone acetonide in the treatment of facial melasma.

Participants

Adults aged ≥ 18 years of either sex with clinically diagnosed melasma confirmed under Wood's lamp examination were eligible.

Exclusion Criteria: Included pregnancy or lactation, history of topical depigmenting treatment within 3 weeks before enrolment, or the presence of uncontrolled diabetes, polycystic ovarian disease, or obesity. Participants provided **written informed consent**, and the study protocol was approved by the Institutional Ethics Committee.

Randomisation and Blinding

Participants fulfilling eligibility criteria were randomly assigned in a 1:1 ratio to receive either cysteamine or triple-combination therapy using a computer-generated random number table. Allocation concealment was maintained using opaque sealed envelopes. Both investigators and participants were blinded to the treatment allocation. The study creams were dispensed in identical unlabelled containers coded by a pharmacist not involved in data collection or analysis.

Intervention

Participants in Group A applied 5 % cysteamine cream once daily at night on affected facial areas, whereas Group B received the triple-combination cream with identical instructions. Both groups were counselled on strict photoprotection and the use of broad-spectrum sunscreen during the study period. Treatment was continued for 12 weeks, with clinical assessments at baseline, week 4, week 8, and week 12. Compliance was monitored by self-report and measurement of returned product.

Outcome Measures

The primary outcome was the change in modified Melasma Area and Severity Index (mMASI) from baseline to week 12.

Sample Size Calculation

The proportion of Cysteamine and MKF in grading of improvement in pigmentation in both groups assessed by the investigators and patients was reported as 0.51 and 0.48 by Maryam Karrabi1 et al. (2020) in the edition the Journal of Skin Research and Technology. Based on this guide, assuming a 95% confidence interval, estimated risk difference of 0.034, population risk of 0.2 and two-tailed test assuming follow the normal distribution. The minimum required sample size will be 48 ~50. Consider 25 for each group.[10]

$$n = \frac{Z^2_{1-\frac{\alpha}{2}}\,[P(1-P_1)+P(1-P_2)]}{d^2}$$

Data Collection and Assessment

At baseline, demographic and clinical variables—including age, gender, Fitzpatrick skin type, family history, disease duration, oral contraceptive use, pregnancy history, smoking status, and triggering factors such as sun exposure—were recorded. Laboratory tests included fasting blood glucose, serum insulin, and lipid profile.

Disease severity was scored by a single blinded dermatologist using the mMASI scale. Subjective improvement and quality-of-life impact were assessed using the MELASQOL score System questionnaire at each visit.

Statistical Analysis: All data were entered into a secured database and analysed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies or percentages. Comparisons between groups were performed using the independent t-test for continuous data and the χ^2 test for categorical variables. Z- test for proportion were used to compare categorical variables in baseline characteristics.

RESULTS

As shown in Table 1, both treatment groups were comparable at baseline, with no statistically significant differences in demographic or clinical

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variables. The average age was 36.2 ± 7.4 years for the cysteamine group and 35.8 ± 8.1 years for the triple combination (TC) group (p = 0.86). Most of the people who took part were women (88% in both groups) and had Fitzpatrick skin type IV (80% and 76%, respectively). The average length of melasma, family history, and starting mMASI and MELASQOL scores were about the same for both groups. This shows that the groups were properly randomised and that the starting scores were the same. Table 2 shows that the mean mMASI scores for both the cysteamine and TC groups went down steadily from baseline to week 12. From week 8 onwards, the difference became statistically significant in favour of cysteamine (mean ± SD: 7.24 ± 2.46 vs. 8.65 ± 2.57; p = 0.04) and stayed that way at week 12 (5.19 ± 1.98 vs. 6.49 ± 2.16; p = 0.01). This means that cysteamine worked better to improve pigmentation severity.

Table 3 shows that the MELASQOL scores for both groups went down steadily over the study period. This shows that psychosocial well-being improved. Although initial changes were not statistically significant, cysteamine demonstrated a markedly greater reduction by week 12 (18.7 ± 4.2 vs. 21.1 ± 5.1; p = 0.028), indicating a superior effect on patient satisfaction and disease burden. Table 4 shows that the TC group had more side effects (56%) than the cysteamine group (24%). Erythema, burning, and peeling were the most common side effects. They were mild and went away quickly. No participant discontinued therapy due to adverse effects. Overall, cysteamine showed a better safety and tolerability profile compared to the TC regimen. Status of melasma improvement before and after treatment was shown in figure 1 and figure 2.

Table 1: Baseline Characteristics of the study participants

Variable	Cysteamine (n = 25) Mean ± SD / n (%)	Triple Combination (n = 25) Mean ± SD / n (%)	p-value
Age (years)	36.2 ± 7.4	35.8 ± 8.1	0.86
Female sex	22 (88.0 %)	22 (88.0 %)	1
Fitzpatrick skin type IV	20 (80.0 %)	19 (76.0 %)	0.78
Duration of melasma (years)	3.8 ± 2.1	3.9 ± 2.4	0.88
Family history positive	10 (40.0 %)	9 (36.0 %)	0.76
Baseline mMASI	13.42 ± 3.21	13.67 ± 3.14	0.79
Baseline MELASQOL	34.6 ± 5.3	33.9 ± 5.7	0.63

Table 2: Comparison of Modified MASI Scores Between Groups Over 12 Weeks

Time Point	Cysteamine (Mean ± SD)	Triple Combination (Mean ± SD)	Mean Difference (95 % CI)	t-value	p-value
Baseline	13.42 ± 3.21	13.67 ± 3.14	−0.25 (−2.04 – 1.54)	0.27	0.78
Week 4	10.14 ± 2.94	11.25 ± 2.88	−1.11 (−2.55 – 0.33)	1.56	0.18
Week 8	7.24 ± 2.46	8.65 ± 2.57	−1.41 (−2.78 – −0.04)	2.11	0.05*
Week 12	5.19 ± 1.98	6.49 ± 2.16	−1.30 (−2.26 – −0.34)	2.72	0.03*

Table 3: Comparison of MELASQOL Scores Between Groups Over 12 Weeks

Time Point	Cysteamine (Mean ± SD)	Triple Combination (Mean ± SD)	Mean Difference (95 % CI)	t-value	p-value
Baseline	34.6 ± 5.3	33.9 ± 5.7	0.7 (−2.1 – 3.5)	0.49	0.655
Week 4	28.1 ± 4.8	29.5 ± 5.2	−1.4 (−3.9 – 1.1)	1.09	0.328
Week 8	22.6 ± 4.3	24.3 ± 4.8	−1.7 (−3.6 – 0.2)	1.85	0.193
Week 12	18.7 ± 4.2	21.1 ± 5.1	−2.4 (−4.5 – −0.3)	2.27	0.028*

Table 4: Adverse Events among study participants

Adverse Event	Cysteamine n (%)	Triple Combination n (%)
Erythema	3 (12 %)	6 (24 %)
Burning / Stinging	2 (8 %)	7 (28 %)
Peeling	1 (4 %)	5 (20 %)
Any adverse event	6 (24 %)	14 (56 %)

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Figure 1a: Status of Melasma before Cysteamine cream usage

Fig 1b: Melasma improvement after Cysteamine cream usage

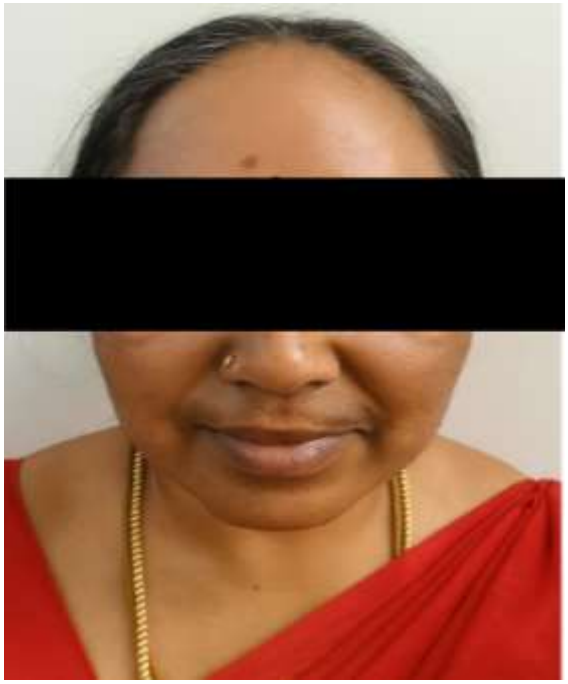

Figure 2a: Status of Melasma before Triple combination cream

Figure 2a: Melasma improvement after Triple combination cream usage

DISCUSSION

This double-blinded randomised controlled trial comparing 5% cysteamine cream with the fluocinolone–hydroquinone–tretinoin triple-combination (TC) cream done by Mawu FO et al showed that both treatments significantly improved pigmentation severity (mMASI) over 12 weeks. However, cysteamine showed a better reduction starting in week 8, with fewer side effects and higher patient satisfaction. Our results align with several recent randomised controlled trials (RCTs) and systematic reviews indicating that cysteamine exhibits efficacy similar to hydroquinone-based treatments while offering a superior safety profile. A 2024 meta-analysis of seven RCTs showed that cysteamine 5% worked better than a placebo (SMD = –0.84, $p < 0.00001$) and that there was no statistically significant difference between cysteamine 5% and

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hydroquinone 4% (SMD = 0.16, p = 0.42). This proved that the two drugs were equally effective.[11] A quasi-randomized controlled study from Taiwan comparing 5% cysteamine with 4% hydroquinone + 0.06% betamethasone for 12 weeks reported mMASI reductions of 37.9% (p = 0.009) and 33.1% (p = 0.009), respectively, with no significant inter-group difference but fewer side effects in the cysteamine arm.[12] Similarly, a 2025 Indonesian double-blind RCT comparing 5 % cysteamine + ectoine with 4 % hydroquinone + ectoine reported equivalent efficacy in mMASI and MELASQoL scores (p > 0.05).(13)Earlier work by Maryam Karrabi et al. compared cysteamine 5 % to modified Kligman's formula (MKF), showing comparable investigator- and patient-rated improvement (~51 % vs 48 %) and similar tolerability.[14] These results are similar to what the current trial found: cysteamine was much better at 8–12 weeks. This suggests that cysteamine may work faster and cause fewer irritant reactions. Contemporary literature and our findings indicate that 5% cysteamine provides similar depigmenting efficacy to hydroquinone-based triple combination therapy, with enhanced tolerability, making it particularly suitable for long-term or maintenance therapy in patients with darker phototypes or those who are intolerant to hydroquinone. Cysteamine's antioxidant and anti-tyrosinase properties may provide protective effects against oxidative melanogenesis.[15]

CONCLUSION

This randomised, double-blind controlled trial showed that 5% cysteamine cream is a good and safe alternative to the standard fluocinolone–hydroquinone–tretinoin triple-combination cream for treating facial melasma. Both treatment groups showed significant improvement in pigmentation and quality of life over 12 weeks; however, cysteamine achieved greater reduction in pigmentation severity from week eight onwards with markedly fewer adverse effects. Cysteamine presents a promising hydroquinone-free alternative for both initial and maintenance therapy of melasma, particularly for individuals with darker skin phototypes or those who are intolerant to hydroquinone-based treatments, due to its comparable efficacy, enhanced safety, and greater patient acceptability.

Limitations: The study's main limitations include a relatively small sample size and short follow-up period, which may not fully capture long-term efficacy and recurrence. Larger multicentre studies with extended follow-up are needed to confirm these findings.

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