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Efficacy of overnight leave-on sandwich therapy with 5% cysteamine and ectoine cream compared to hydroquinone 4% cream for treatment of melasma: a double-blind randomized controlled trial

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Abstract

Introduction: Melasma is a common hypermelanosis presenting as dark patches on sun-exposed skin. Its treatment remains challenging due to slow response, especially in chronic cases. This study compares the efficacy of 5% cysteamine with ectoine cream versus 4% hydroquinone with ectoine cream in treating melasma.
Methods: A double-blind randomized controlled trial was conducted from January to March 2024 across three centers in Indonesia: Dr. Moewardi Hospital (Surakarta), Gatot Soebroto Army Hospital (Jakarta), and Dr. Saiful Anwar Hospital (Malang). Participants were randomly assigned to Group A (5% cysteamine + ectoine) or Group B (4% hydroquinone + ectoine). Efficacy was evaluated using the modified Melasma Area and Severity Index (mMASI) and the JANUS-I skin analyzer. Quality of life was assessed using Melasma Quality of Life Scale (MELASQoL) and Dermatology Life Quality Index (DLQI) questionnaires.
Results: Both groups demonstrated reduced mMASI and JANUS-I scores, with slightly greater improvement in Group A, although the difference was not statistically significant ($p > 0.05$). Quality of living also improved in both groups, with no significant difference between them ($p > 0.05$).
Conclusions: Both treatment regimens effectively improved melasma pigmentation and QoL. Either 5% cysteamine with ectoine or 4% hydroquinone with ectoine can be considered viable treatment options for melasma.

Keywords: cysteamine, hydroquinone, therapeutic, quality of life, melasma

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Introduction

Melasma is a form of hypermelanosis characterized by dark patches on sun-exposed skin, particularly the face (1, 2). It is more prevalent in individuals with darker skin tones and is more commonly observed in women (1). Globally, the prevalence of melasma is approximately 1% (3). Although it is benign, its facial involvement can cause cosmetic concerns, potentially leading to psychological distress in affected individuals (4).

Treating melasma remains a challenge for clinicians due to its slow response, particularly in chronic cases (5). Effective therapies primarily involve the use of depigmenting agents. Hydroquinone, a widely studied and commonly used tyrosinase inhibitor, is considered the gold standard for melasma treatment (6). Other treatment options include tranexamic acid, vitamin C, corticosteroids in combination with other agents, and topical retinoids (4). However, long-term hydroquinone use carries risks, such as exogenous ochronosis (7). Therefore, alternative depigmenting agents with comparable or superior efficacy and fewer side effects are needed.

Cysteamine is a relatively new pigment-lightening agent with limited research, particularly in the treatment of melasma. It is an aminothiol compound naturally present in human cells (8). Previous studies have demonstrated promising results for cysteamine in melasma treatment compared to placebo (9, 10). Ectoine, a hydrating agent, is often used alongside cysteamine to reduce irritation. However, there is still a lack of studies directly comparing the efficacy of cysteamine with hydroquinone. This double-blind randomized controlled trial evaluates and compares the effectiveness of cysteamine and hydroquinone as treatments for melasma.

Methods

All subjects in this study were female. This study was a randomized-controlled trial, double blind. A total of 80 women with facial melasma were included in this study and were divided into two groups: a group with 5% cysteamine cream and ecto-derm® (ectoine) cream application (Group A) and a group with 4% hydroquinone cream and ectoine cream application (Group B). Subjects were recruited from three research centers in Indonesia: Dr. Moewardi General Hospital (Surakarta), Gatot Subroto Army Central Hospital (Jakarta), and Dr. Saiful Anwar Regional General Hospital (Malang). This study was approved and registered at the Human Research Ethics Committees Dr. Moewardi General Hospital (no. 1.242/VII/HREC/2023). The study was conducted from January to March 2024.

The inclusion criteria for this study were women over 18 years old, with a history of melasma for at least 3 months, and Fitzpatrick skin types III–V. Exclusion criteria included pregnancy, breastfeeding, menopause, and previous depigmentation therapy within the 6 months prior to the study. Eligible participants were randomly assigned to one of the two groups using a computer application (https://randomize.net/). The blinding process was implemented for all subjects, evaluators, and analysts, ensuring that none of the parties

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knew whether a participant was assigned to Group A or Group B.

Before applying the cysteamine and hydroquinone creams, subjects were instructed to use ectoine cream for Group A and placebo cream for Group B on the entire face in the morning. Following this, all participants applied SPF 30 sunscreen. In the evening, subjects in Group A applied ectoine cream on the entire face, followed by 5% cysteamine cream, which was left on overnight. In Group B, subjects applied ectoine cream on the entire face, followed by 4% hydroquinone cream, also left overnight, similar to Group A. Therapeutic efficacy was evaluated using the modified Melasma Area and Severity Index (mMASI) score and JANUS-I skin analyzer (PIE Co., Gyeonggi-do, Republic of Korea) scores. The impact on quality of life was assessed using the Melasma Quality of Life Scale (MELASQoL) and Dermatology Life Quality Index (DLQI) questionnaires. Evaluations were conducted on days 0, 28, and 56 (D-0, D-28, D-56). Demographic data, including age, skin phototype, disease duration, and family history of melasma, were also collected.

Statistical analysis was performed using IBM SPSS version 20 (Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant. The comparison of efficacy between the two groups was conducted using the t-test or Mann–Whitney test, with data presented as mean ± standard deviation (*SD*).

Results

A total of 77 subjects completed the study, with 40 subjects in Group A and 37 subjects in Group B (Fig. 1). The demographic characteristics of both groups are presented in Table 1.

Baseline values for all parameters showed no significant differences between the groups. Melanin parameters did not differ significantly at assessments D-28 and D-56 (p > 0.05). However, melanin levels decreased in Group A (cysteamine), whereas they increased in Group B (hydroquinone). Melanin parameters were measured using a Mexameter® (Courage+Khazaka, Köln, Germany). The increase in melanin index in Group B may be attributed to photodamage from ultraviolet radiation because some patients had a history of sun exposure, which could elevate the melanin index at the time of measurement (11). The erythema parameter showed a significant difference between the two groups at assessment D-56 (p = 0.021). However, no statistically significant difference in the melanin parameter was observed between the groups at D-56 (p = 0.37).

The main efficacy parameters, mMASI and JANUS-I scores, showed no statistically significant difference between the two groups (p > 0.05). Both mMASI and JANUS-I scores decreased in both groups, with a greater reduction observed in Group A. Quality of life parameters, assessed using MELASQoL and DLQI, also showed no significant difference between the groups (p > 0.05). Both groups experienced a reduction in MELASQoL and DLQI, indicating an improvement in quality of life. Overall, no statistically significant difference was found in any assessment parameters between Group A (5% cysteamine) and Group B (4% hydroquinone; Table 2, Fig. 2).

Representative images of patients before and after treatment are shown in Figures 3 and 4.

Table 1 | **Demographic characteristics of subjects.**

Characteristics	Group A (n = 40)	Group B (n = 37)
Age, years ± *SD*	41.2 ± 6.8	42.7 ± 8.1
Skin phototype, *n* (%)		
III	3 (7.5)	2 (5.4)
IV	28 (70.0)	26 (70.3)
V	9 (22.5)	9 (24.3)
Disease duration, years ± *SD*	6.4 ± 1.2	6.2 ± 1.8
Family history of melasma, *n* (%)	10 (25.0)	9 (24.3)

SD = standard deviation.

Table 2 | **Study outcomes.**

Parameters	Group A (n = 40), mean ± *SD*	Group B (n = 37), mean ± *SD*	p-value
Melanin			
D-0	234.66 ± 69.46	219.95 ± 64.64	0.34
D-28	224.73 ± 64.22	226.30 ± 54.24	0.91
D-56	221.75 ± 68.37	235.96 ± 68.93	0.37
Erythema			
D-0	329.33 ± 75.96	309.90 ± 81.93	0.34
D-28	334.19 ± 78.41	337.43 ± 78.63	0.75
D-56	333.56 ± 86.84	375.74 ± 82.16	0.021*
mMASI			
D-0	5.45 ± 3.69	5.46 ± 4.01	0.75
D-28	4.37 ± 3.26	4.79 ± 3.53	0.49
D-56	3.81 ± 3.32	4.01 ± 3.32	0.67
JANUS-I			
D-0	4.60 ± 1.74	5.45 ± 1.74	0.17
D-28	4.18 ± 2.26	4.69 ± 0.87	0.88
D-56	3.35 ± 1.49	4.41 ± 0.77	0.71
MELASQoL			
D-0	2.45 ± 1.45	2.91 ± 1.08	0.62
D-28	2.24 ± 1.33	3.04 ± 1.12	0.56
D-56	2.02 ± 1.27	3.31 ± 1.23	0.58
DLQI			
D-0	5.21 ± 6.21	6.83 ± 3.93	0.53
D-28	4.75 ± 5.25	5.60 ± 3.60	0.40
D-56	3.35 ± 4.53	5.40 ± 3.53	0.76

mMASI = modified Melasma Area and Severity Index, MELASQoL = Melasma Quality of Life Scale, DLQI = Dermatology Life Quality Index, D = day, *SD* = standard deviation.
*Statistically significant.

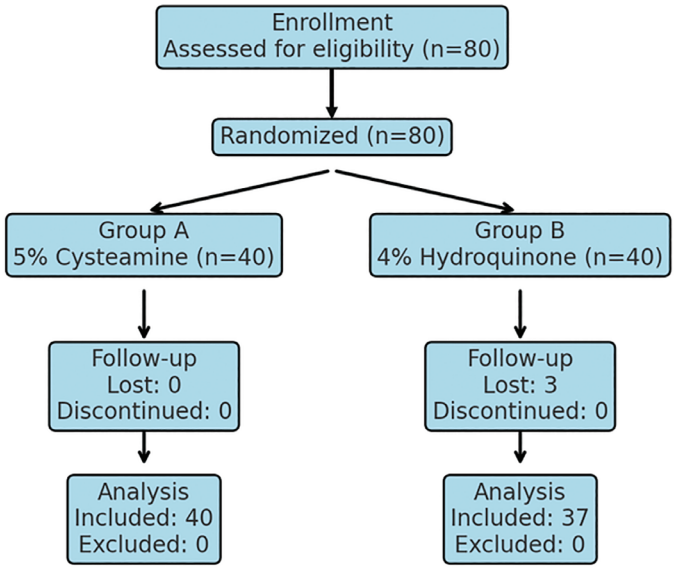

Figure 1 | Study flow diagram.

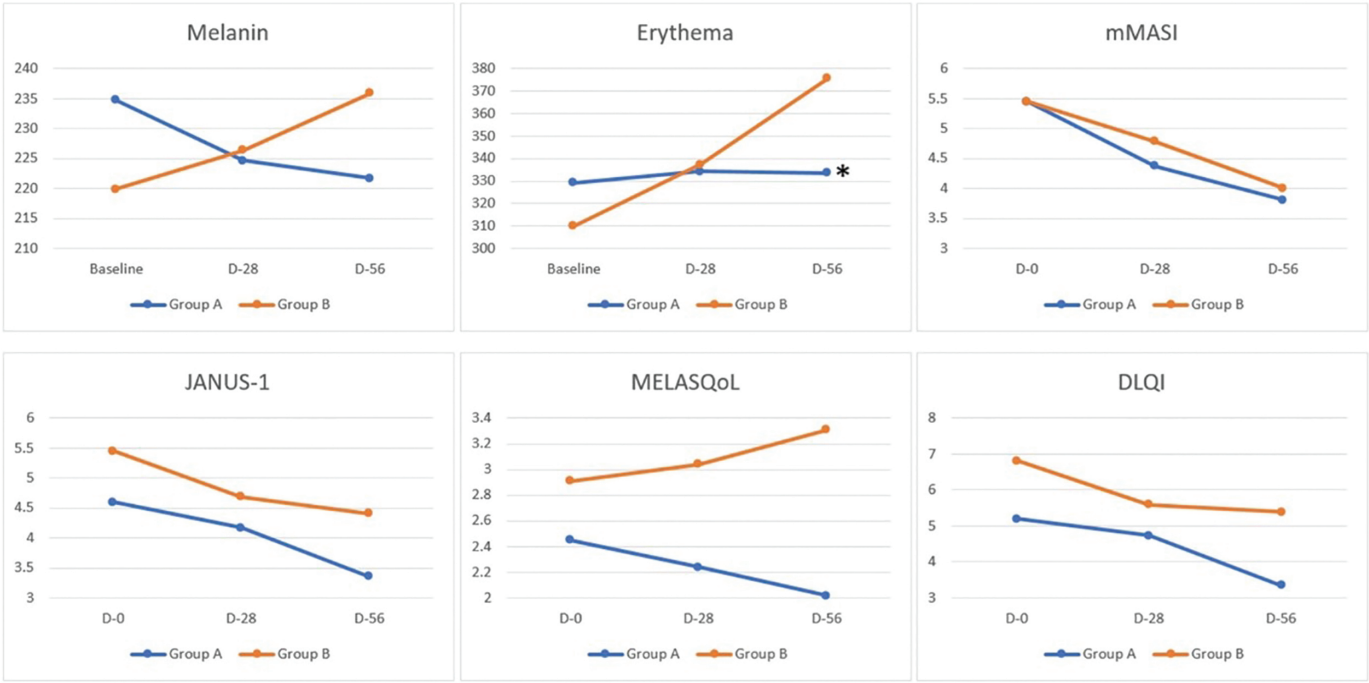

Figure 2 | Graph of research results; *statistically significant.
mMASI = modified Melasma Area and Severity Index, MELASQoL = Melasma Quality of Life Scale, DLQI = Dermatology Life Quality Index.

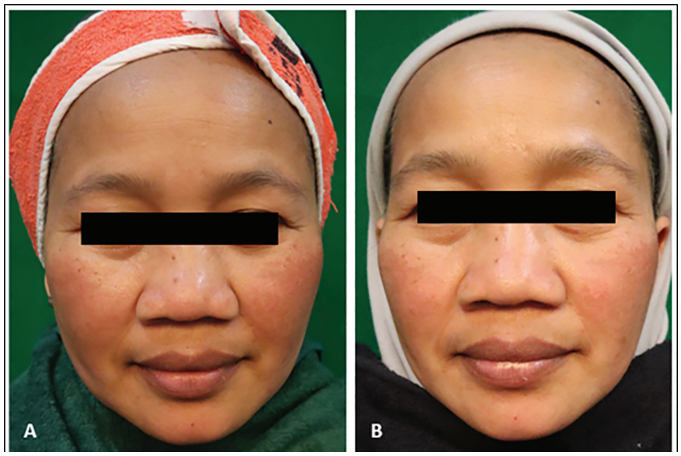

Figure 3 | Patient A11 (A) before intervention and (B) after intervention.

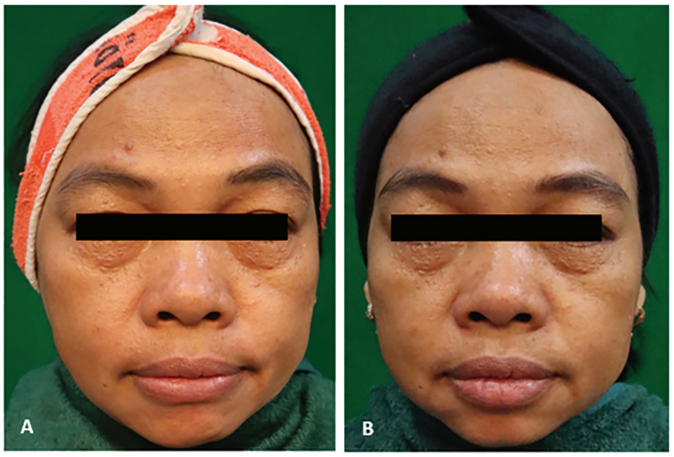

Figure 4 | Patient B1 (A) before intervention and (B) after intervention.

Discussion

Various treatments are available for melasma today, yielding varying results. These treatments are generally categorized into systemic and topical therapies. Examples of systemic therapies include tranexamic acid, *Polypodium leucotomos* extract, vitamin C, and vitamin E (12). Cysteamine and hydroquinone, which were compared for efficacy in this study, are both topical therapies. Hydroquinone is considered the first-line treatment for melasma due to its proven effectiveness and good tolerance (6, 13–15). Hydroquinone acts as a depigmenting agent by inhibiting the enzyme tyrosinase, which plays a crucial role in melanin production in the skin. Inhibition of this enzyme by hydroquinone prevents the conversion of the amino acid tyrosine into melanin precursors (16).

Although hydroquinone has proven effective in treating melasma, it also presents several adverse effects on the skin. These side effects include irritant contact dermatitis, itching, erythema, and dry skin (17). The most concerning side effect of hydroquinone use is exogenous ochronosis, which results from the accumulation of homogentisic acid in the skin (16, 18). As a result, there is a need for alternative therapies that offer similar efficacy while minimizing the side effects associated with hydroquinone. This trial has confirmed the effectiveness of both cysteamine and hydroquinone for managing melasma. Both treatments demonstrated comparable efficacy in treating facial melasma. These findings suggest that cysteamine could be a viable alternative therapy for melasma.

The results of this study demonstrated similar efficacy across all parameters, including mMASI score, JANUS-I skin analyzer, and quality of life measures such as MELASQoL and DLQI. The only exception was erythema, which showed a more significant improvement with cysteamine. In this trial, the cysteamine cream was applied using a sandwich technique, whereby ectoine cream was applied beneath the cysteamine layer and left on overnight. This technique was chosen to minimize irritation caused by cysteamine. A previous study by Nguyen et al. reported that topical cysteamine has comparable efficacy to hydroquinone for melasma treatment. Although cysteamine caused more side effects, these were generally mild to moderate, including erythema, dryness, itching, burning, and irritation (4). Another study by Lima et al. found that topical 5% cysteamine was both safe and effective for treating melasma, although it yielded inferior results compared to 4% hydroquinone (7). The use of the sandwich technique with cysteamine has also been reported in a study by Anwar et al., in which tranexamic acid was applied under cysteamine. This com-

bination resulted in satisfactory outcomes, with significant reductions in both mMASI and Mexameter® scores (19).

In this study, mMASI and JANUS-I scores showed a decline as the study progressed, with the lowest mMASI and JANUS-I scores observed on D-56. Quality of life scores using MELASQoL and DLQI also showed a decrease as the study progressed. This shows that, along with clinical improvement, the use of cysteamine has an impact on improving the quality of life of melasma patients. Cysteamine is an aminothiol compound that is formed due to the degradation of coenzyme A (20). Cysteamine works as a depigmenting agent in a similar way as hydroquinone, by acting as a tyrosinase inhibitor. The fundamental difference between cysteamine and hydroquinone in their mechanism as depigmenting agents is that cysteamine causes inhibition of melanogenesis, whereas hydroquinone causes melanocytotoxicity (21). Daniel et al. conducted a similar study in 2021 on melasma patients using 5% cysteamine night cream, previously applied with moisturizer, and sunscreen during the day. The results showed that leaving the cream on overnight is safe for patients that prefer not to wash it out (22).

This study has several limitations. First, it did not assess side effects, which means that the safety and tolerability of cysteamine could not be evaluated. Second, the sample size in this study was relatively small.

Conclusions

This study demonstrates that topical 5% cysteamine is equally effective as 4% hydroquinone in managing facial melasma. The use of 5% cysteamine may result in clinical improvements and an enhanced quality of life for patients with melasma.

Acknowledgments

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