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Original Article

The effectiveness of topical cysteamine in treating melasma: A systematic review and meta-analysis

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Abstract

Background Melasma is a hyperpigmentation disorder in the form of a light brown to blackish macula with irregular edges that are often exposed to sunlight, especially the face. The causes of melasma are still not widely understood and the treatment remains a challenge. Topical cysteamine recently has been studied as a promising depigmenting agent in treating melasma. This study aimed to compare the effectiveness of cysteamine cream in treating melasma towards mainstay therapy, hydroquinone (HQ).

Methods Online searching on Pubmed-MEDLINE, Scopus, EBSCOhost, ProQuest, and Cochrane Library databases found 3 relevant articles included in this systematic review and meta-analysis (n=128). The outcome measured was mMASI and MELASQoL scores.

Results The meta-analysis showed a reduction in mMASI score by week 8 (SMD=0.33(95% CI -0.02 - 0.68), p=0.92, I^2=0%) and week 16 (SMD=0.13(95% CI -0.02 - 0.48), p=0.89, I^2=0%) in both cysteamine and control groups. The meta-analysis also demonstrated a reduction in MELASQoL score (SMD=0.23(95% CI -0.16 - 0.62), p=0.16, I^2=50%) compared with baseline.

Conclusion Results revealed that both 5% cysteamine and 4% HQ cream had similar favorable efficacy in treating melasma and also increasing melasma patient's quality of life .

Key words
Melasma; Cysteamine; Hydroquinone.

Introduction

Melasma is a hyperpigmentation disorder in the form of a light brown to blackish macula with irregular edges, symmetrical in shape, and hitting areas that are often exposed to sunlight, especially the face. The term melasma comes from the Greek 'melas' which means black, or also called chloasma which comes from the Greek 'chloazein' which means to be green.[1,2] Melasma can occur in all races but is most common in dark-skinned individuals in the Fitzpatrick IV, V, and VI skin types commonly found in Hispanics, Africans, and Asians.[3] The prevalence of melasma ranges from 9% of Latin women in South America to 40% of women in Southeast Asia.[2,4] Melasma is more about women between the ages of 20 to 40 and can hit fewer men.[5]

The causes of melasma are still not widely understood, among several factors are endocrine, genetic, sunlight radiation, and idiopathic.[1,6] The presence of melasma interferes with facial

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appearance and tends to be difficult to treat and easily recurrent.[7,8] Assessment of the severity of melasma becomes important to help determine the therapy plan, estimate the prognosis, as well as evaluate the therapy. This assessment can be carried out subjectively or objectively. Subjective assessments include the Melasma Area and Severity Index (MASI), Modified Melasma Area and Severity Index (mMASI), Melasma Severity Scale (MSS), and Melasma Severity Index (MSI). While objective assessment can use chromameter, Mexameter®, photography with polarized rays, computer-measured Wood lights, and Dermacatch®.[9,10] Currently both MASI scores and mMASI scores are the most frequently used parameters and have been tested for reliability and validity as guides in melasma clinical research.[9,11] In addition to the assessment of severity, the presence of skin diseases such as melasma also causes physical and psychosocial disorders that can make significant emotional changes such as feelings of distraction, frustration, shame to depression. Therefore, the assessment of the quality of life is important and influential in the plan and success of therapy. This assessment was conducted using the MELASQoL (Melasma Quality of Life) score instrument which consists of 10 questions about what is felt about melasma and has been widely translated into various languages.[12]

A wide selection of therapeutic modalities for melasma is available through oral and topical drug administration, as well as procedural procedures.[13] To date there has been no single agent or universally effective melasma treatment procedure.[14,15]

Hydroquinone (HQ) is a first-line topical depigmentation agent in the treatment of melasma.[16–18] The effects of depigmentation by HQ are related to its melanocytotoxic effects, but this ability is not specific to melanocytes alone so it can hit other epidermal cells such as keratinocytes. In addition, this agent often causes mild to moderate side effects such as allergic and irritant contact dermatitis, and long-term use can give rise to exogenous ochronosis.[16,19,20] Therefore in some countries the use of hydroquinone is prohibited as a depigmentation agent. Researchers began looking for depigmentation agents that had equivalent effectiveness to hydroquinone but with more minimal side effects, one of which is cysteamine.

Cysteamine hydrochloride (β-mercapto ethylamine hydrochloride) is a potential depigmentation molecule that has been known since 4 decades ago.[21] In 1966, Chavin *et al.* first conducted a study by injecting intradermal cysteamine into the skin of black goldfish and obtaining significant skin depigmentation results.[22] Then the study was continued by Bleehen *et al.* by administering topical cysteamine on the skin of mammals (black guinea pigs) which reported potential depigmentation which was higher by cysteamine than hydroquinone.[23] Subsequent research was conducted by Mansouri *et al.* comparing cysteamine to placebo. In this study, cysteamine showed significant efficacy as a depigmentation agent against melasma with a significant decrease in MASI scores compared to placebo.[21] Other studies using cysteamine against cell cultures also proved that this molecule works by inhibiting melanogenesis and is not melanotoxic in depigmenting melanocytes so it is considered safer.[24] Systematic review studies of cysteamine also found that this agent is more effective than the vehicle has the same effectiveness as MFK and can be an alternative to MFK and its respective components.[25] Side effects that can arise are mild such as erythema, dryness of the skin, and itching that subsides after one week, and no exogenous ochronosis is found in long-term use.[10,21] Based on the results of published

studies, the authors are interested in conducting a systematic review and meta-analysis about the effectiveness of topical cysteamine in treating melasma using the assessment of mMASI scores and MELASQoL scores parameters.

Material and Methods

Data searches were conducted online through Pubmed-MEDLINE, Scopus, EBSCOhost, ProQuest, and Cochrane Library with a timeframe until analysis was carried out based on the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flowchart. The following MeSH terms were used for searching: "cysteamine" AND "melasma".

Three reviewers conducted the study selection independently. Duplicate articles were removed. The title and abstract, as well as the full text, were reviewed for eligibility using the predefined inclusion and exclusion criteria. Differences in opinion were resolved between all reviewers to settle a consensus.

Data extraction was performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only. Every dispute in determining papers and data extraction was settled with consensus.

The risk of bias from the studies included in the analysis, both qualitatively and quantitatively assessed using The Cochrane Collecting data – form for RCTs only and The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials, including randomization, allocation concealment, blinding of research subjects, blinding outcomes, incomplete outcome data, selection of reported outcomes, and other biases.

Overall statistical analyses were performed using Review Manager Version 5.4 software (The Cochrane Collaboration). Where data was not available to enable pooling, a descriptive synthesis was performed.

Results

The search for research articles was conducted based on the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flowchart **(Figure 1)**. The results of the search found 128 related articles. After checking the title and getting rid of duplication, 14 relevant article titles were obtained. The abstracts of these articles were then reviewed, so 11 articles were excluded, consisting of 3 review articles, 2 systematic reviews, 2 systematic reviews and meta-analyses 4 articles not within the study. Three other research articles were used in qualitative reviews (systematic reviews) and quantitative reviews (meta-analysis) to assess the effectiveness of cystamine as a depigmentation agent in treating melasma using assessment of mMASI scores and MELASQoL scores parameters.

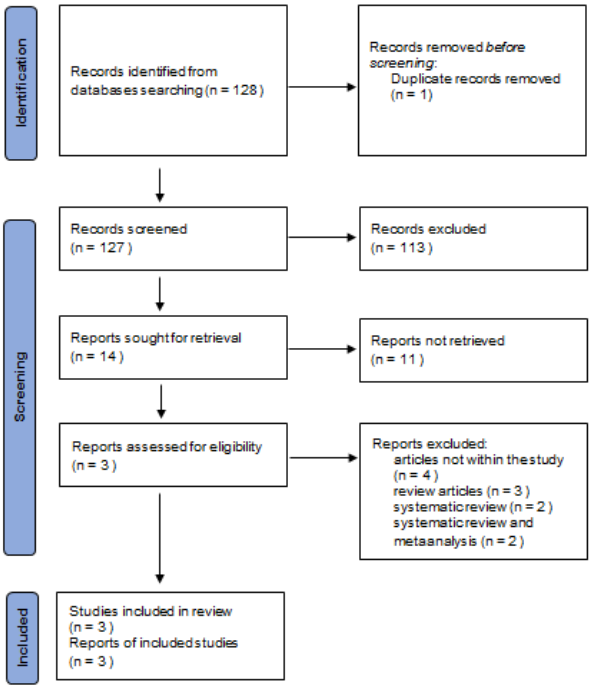

Figure 1 PRISMA Flow Diagram

The majority of the studies were conducted in Iran (n:1), Australia (n:1), and Brazil (n:1) in the 2019-2021 time frame **(Table 1)**. The number of samples included in the study varied from 20-65 research samples. All studies assess clinical improvement subjectively and or objectively. In subjective assessment, all patients were assessed with mMASI scores, while objectively assessed with melanin index, MELASQoL, and IGA.

Therapy in the treatment group was given topical cysteamine 5%, which was given once at night before bedtime, then cysteamine cream was allowed to stand for 15 minutes (can be increased up to 2 hours) then rinsed with water. The study in the control group used topical hydroquinone 4% (n:2) and 4%+3% ascorbic acid hydroquinone cream (n:1) given at night and rinsed the next day. The duration of treatment is 16 weeks (n:3).

Result of Qualitative Data Analysis (Systematic Review)

1. Nguyen dkk, 2019[26]

This study was conducted between May 2019 and March 2020 on 20 melasma patients, randomized controlled and double-blinded to compare the topical use of 5% cysteamine (n=10) with 4% hydroquinone (n=10). The study subjects were aged 18 years and over with a history of melasma for at least 3 months, with exclusion criteria including pregnancy and breastfeeding, facial redness, significant sun exposure (exposure of more than 2 hours per day from outdoor work), topical use of hydroquinone, facial brightening agents, topical steroids, topical retinoic acid, as well as laser therapy on the face in the previous month.

The administration of cysteamine cream is done once at night and allowed to stand for 15 minutes and then rinsed with water, while

Table 1 Characteristics of included studies.

No	*Study*	*Country*	*Sample*	*Population with melasma*		*Study outcome*	*Duration of intervention (weeks)*	*Clinical trial-type*
				Cysteamine group	*Control group*			
1	Nguyen et al, 2020	Australia	20	cysteamine 5% cream	hydroquinone 4% cream	mMASI score, QoL	16	*Randomized, double-blinded, single center*
2	Lima et al, 2020	Brazil	40	cysteamine 5% cream	hydroquinone 4% cream	mMASI, MELASQoL score, Di*L	16	*Quasi-randomized, single-blinded*
3	Sepaskhah et al, 2022	Iran	65	cysteamine 5% cream	hydroquinone 4% + ascorbic acid 3% cream	mMASI, MELASQoL score, Melanin Index, IGA, PGA	16	*Randomized, single-blinded,control trial*

hydroquinone cream is given 1 time every night and allowed to stand all night without rinsing. All patients received sunscreen with SPF 50+ which was used every morning 15 minutes before exposure to sunlight and repeated 40 minutes after swimming or 2 hours after sweating. The study was conducted for 4 sessions, with evaluations in weeks 2 and 4 by telephone to determine compliance and the presence of side effects, and visitation was carried out in weeks 8 and 16 to determine compliance, side effects, facial examinations, mMASI and clinical photos of patients. Evaluation of Quality of Life (QoL) was also carried out in the 16th week.

The outcomes analyzed were differences in mMASI scores before and after treatment at weeks 8 and 16 in the cysteamine and hydroquinone groups. The baseline mean of mMASI in the cysteamine group was 7.1±3.41, and the hydroquinone group was 9.2±5.7. The results of the study in week 8 obtained a decrease in the mean mMASI score, in the cysteamine group by 6.0±2.2 (15.7% reduction) and in the hydroquinone group by 5.7±4.2 (37.9% reduction). In week 16, another analysis was carried out where there was a continuation of the decrease in the mean mMASI in the cysteamine group by 5.6±2.7 (21.3% reduction from the baseline) and in the hydroquinone group by 6.3±4.8 (32% reduction from the baseline). In the analysis per group, a greater decrease in scores was found against the baseline in the cysteamine group in week 16, namely 3.1±1.9 (39.1%) compared to the hydroquinone group of 3.2±3.7 (33%). However, the difference between the two groups is not statistically meaningful (P=0.3).

Side effects arising in the cysteamine group include mild moderate irritation, burning, itching, and redness as soon as the cream is applied to the face. While the hydroquinone group includes irritation, dryness, redness, and itching. QoL in both groups experienced improvements marked by an increase in QoL scores in week 16.

2. Lima *et al.* 2019[27]

This study was conducted from October 2019 to February 2020 on 40 melasma patients, quasi-randomized, multicenter, parallel, evaluator-blinded to compare the efficacy and safety of using cysteamine 5% cream (n=20) with hydroquinone 4% cream (n=20). The subjects of the study were women aged 30 to 55 years who had skin phototypes II to V. Patients were also not pregnant, had not menopause, had no other skin diseases on the face, and were not currently receiving skin lightening therapy for melasma at least 1 month earlier (except sunscreen). Cysteamine cream (Clarite Cysteamin, Dermage, Sao Paulo-Brazil) is applied on the face at night and allowed to stand for 15 minutes on the first day then progressively increased to 2 hours if no irritation is obtained the next night. While in the hydroquinone group, 4% hydroquinone cream was given which was applied before going to bed at night and allowed to stand all night then continued to rinse the next day. All patients get sunscreen with SPF 50+.

The study was conducted in as many as 2 sessions which were evaluated on the 60th and 120th days. The outcomes assessed included mMASI scores, Melasma Quality of Life Scale (MELASQoL), and differences in shine with colorimetric (Dif*L) between melasma skin and surrounding skin (<2 cm) using CR-400 Chroma Meter (Konica Minolta). In addition, skin differences were also assessed through standardized photos using The Global Aesthetic Improvement Scale (GAIS) on the T0th and T120th days. Patient adherence was also assessed on days 60 and 120 by evaluating the duration of toleranccysteamineamine (15

minutes to 2 hours), the number of days in the week for cream smearing, and the frequency of sunscreen use. Side effects such as facial erythema, squama, and burning sensation were also assessed on days 60 and 120.

The results of the study provided data on a decrease in mMASI and MELASQoL scores and improvements through photos of 74%. The median baseline of mMASI in the cysteamine group was 9 (6-12), and the median mMASI in the hydroquinone group was 6 (3-8). On day 60, the median mMASI in the cysteamine group was 6 (4-11) or decreased by 24% (15-33%), and the median mMASI in the hydroquinone group was 3 (2-4) or decreased by 41% (31-51%). Furthermore, on the 120th day evaluation, the mean mMASI in the cysteamine group was 5 (4-8) or decreased by 38% (32-45%), and the median mMASI in the hydroquinone group was 2 (1-3) or decreased by 52% (43-61%). The mMASI scores decreased progressively over time in both groups, although a faster decline was obtained in the hydroquinone group. The MELASQoL score also showed progressive declines in both groups where a larger decline was seen in the hydroquinone group after 120 days (P=0.018). Colorimetric examination showed the presence of progressive depigmentation in both groups with insignificant differences (P > 0.160).

Local side effects of erythema and burning sensation are common in the cysteamine group, although the frequency between groups does not differ much (P > 0.170). No severe side effects were obtained from either group.

3. Sepaskhah dkk, 2019[27]

This study was conducted in a single-blind, randomized, controlled manner from 2017 to 2019 on 80 melasma patients to assess the efficacy and effect of cysteamine cream 5% compared to hydroquinone 4%/ ascorbic acid 3% cream (HC). The subjects of the study were patients aged 18-50 years who had epidermal melasma (confirmed with Wood's lamp) for more than 6 months. The patient is also not pregnant or breastfeeding; taking the contraceptive pill for or 3 months before the study; not being on treatment with oral or topical corticosteroids; not currently using other depigmentation agents on melasma lesions during and 3 months before the study; have intolerances such as severe irritation to hydroquinone, ascorbic acid or cysteamine; as well as other pigment abnormalities.

A total of 80 patients were divided into 2 groups, of which there were 31 patients in the cysteamine group and 34 patients in the HC group who followed the study to the end. Cysteamine cream (Scientis SA) is applied on the face once a day every night for 15 minutes for 4 months. While in the control group was given HC cream (hydroquinone 4% ascorbic acid 3% cream) consisting of a mixture of 2 gr of hydroquinone powder (Merck) and 1.5 gr of ascorbic acid powder (Merck) at 50 gr of vanishing cream (Minoo), which was applied on the face once a day every night for 4 months. All patients get sunscreen with SPF 50.

The study was conducted as many as 2 sessions which were evaluated in the 2nd and 4th months. The outcomes assessed include a decrease in the mMASI score, and melanin index measured by the colorimeter instrument SkinColorCatch (formerly Dermacatch). Other outcomes that were also assessed were The Investigator's Global Assessment (IGA), and Patient's Global Assessment (PGA). Quality of Life is also assessed using Persian version of the Melasma Quality of Life Scale. Side effects from treatment were also assessed and reported during the study.

The baseline mean of mMASI in the cysteamine group was 6.69±2.96, and the hydroquinone group was 6.26±3.25. The results of the study in the 2nd month obtained a decrease in the mean score of mMASI, in the cysteamine group which was 5.74±2.57 and in the hydroquinone group which was 4.38±2.22. In the 4th month evaluation, it was found that the decrease in the mean mMASI results in the cysteamine group was 4.47±2.16 and in the hydroquinone group by 3.87±2.00. In the cysteamine group with a history of insufficiently good response to previous treatment, gave a reduction in mMASI score by 75% (6 out of 8 patients). This score decrease was also found in the group that received HC cream where a reduction in mMASI score was obtained by 85.7% (12 out of 14 patients).

The baseline melanin index in the cysteamine group is 37.72±10.17, and the hydroquinone group is 36.37±10.80. The results of the study in the second month obtained a decrease in the melanin index where in the cysteamine group it was 35.28±13.93 and in the hydroquinone group it was 26.25±12.89. In the fourth month evaluation, a decrease in the melanin index was also obtained, where in the cysteamine group it was 31.47±11.90 and in the hydroquinone group it was 23.16±8.83. The melanin index appeared to show improvement in both groups between baseline and fourth month evaluation, but improvements appeared more pronounced in the HC group.

The baseline of MELASQoL in the cysteamine group was 42.90±18.05, and the hydroquinone group was 41.55±16.84. The results of the study in the fourth month showed a decrease in MELASQoL where in the cysteamine group by 34.96±18.56 and in the hydroquinone group by 33.32±16.60. Quality of Life appeared to show improvement in both groups between baseline and fourth month evaluation, but the differences were not significant between the two groups.

In the cysteamine group, several side effects were obtained such as mild transient erythema, burning, and itching (n=7) that did not interfere with the course of treatment, and other side effects such as moderate erythema and itching which indicated allergic contact dermatitis (n=3) so that the patient did not continue treatment. While the side effects that arise in the hydroquinone group are such as mild temporary itching, the onset of blackheads, photosensitivity and dry lips.

Quantitative Data Result (Meta-Analysis)

1. **Results of Meta-analysis of Topical Cysteamine Effectiveness Based on mMASI Score**

Treatment in both groups was carried out at week 8 and week 16. Differences in mean mMASI scores before and after in the treatment group that got topical cystamine, and the control group that got hydroquinone with or without other additions in week 8 are shown in **Table 2**.

Table 2 Differences in the average mMASI score in the cysteamine and control groups in week 8.

No	*Study*	*Cysteamine*			*Control*		
		Mean±SD		*n*	*Mean±SD*		*n*
		Pre	*Post*		*Pre*	*Post*	
1	Nguyen *et al.* 2020	7.1 ± 3.4	6.0 ± 2.2	10	9.2 ± 5.7	5.7 ± 4.2	10
2	Lima *et al.* 2020	9.0±1.72	6.79±2.03	20	5.74±1.44	3±0.57	20
3	Sepaskhah *et al.* 2022	6.69±2.96	5.74±2.57	31	6.26±3.25	4.38±2.22	34

In **Table 2**, study of Nguyen *et al.* showed both the cysteamine group and the control group after treatment gave a decrease in mMASI scores. The mMASI score before treatment in the cysteamine group was 7.1±3.4 and after treatment it decreased to 6.0±2.2, while the mMASI score before treatment in the control group was 9.2±5.7 and after treatment decreased to 5.7±4.2. Lima *et al.*'s research, 2020 showed a decrease in mMASI scores in both groups with mMASI scores before treatment in the cysteamine group was 9.0±1.72 and after treatment decreased to 6.79±2.03, while the mMASI score before treatment in the control group was 5.74±1.44 and after treatment decreased to 3±0.57. In the study of Sepaskhah *et al.* also showed a decrease in both groups, where the mMASI score before treatment in the cysteamine group was 6.69±2.96 and after treatment decreased to 5.74±2.57, while the mMASI score before treatment in the control group was 6.26±3.25 and after treatment decreased to 4.38±2.22.

The results of the meta-analysis of the effectiveness of topical cystamine compared to the control after treatment at week 8 in melasma patients can be seen in **Figure 2**.

Figure 2 shows the results of metaanalysis of the effectiveness of topical cystamine compared to control to mMASI scores in week 8 of melasma patients. Metaanalysis showed heterogeneity assays comparing topical and control administration were insignificant (p=0.92) with a value of I^2=0%, indicating that the research data used for metaanalysis were homogeneous. Based on this, a fixed-effect model is used in calculating metaanalysis.

The results of a meta-analysis comparing topical cysteamine with 4% topical hydroquinone showed the overall standardized mean difference value of the mMASI score was 0.37 with a CI of 95%, -0.14 to 0.88. This showed that there was a greater decrease in mMASI scores in the control group than the cysteamine group but the difference was statistically insignificant (p=0.16).

The results of a meta-analysis comparing topical cysteamine and 4% topical hydroquinone with other additions showed the overall standardized mean difference value of the mMASI score was 0.30 with a CI of 95%, -0.19 to 0.79. This showed that there was a greater decrease in mMASI scores in the control group than in the cysteamine group but the difference was statistically insignificant (p=0.23).

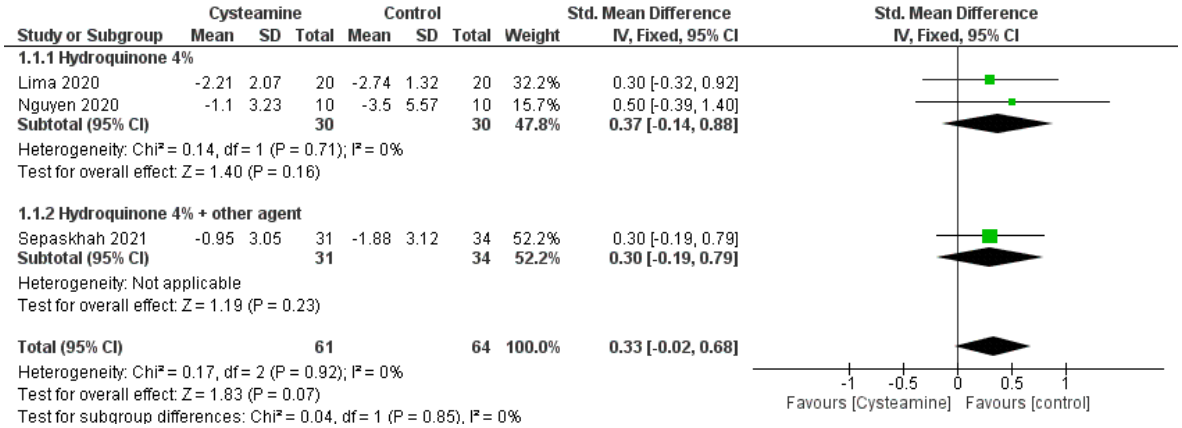

Figure 2 Results of a meta-analysis of the effectiveness of topical cysteamine compared with control to mMASI scores at week 8 in melasma patients.

Table 3 Differences in the average mMASI score in the cysteamine and control groups in week 16.

No	*Study*	*Cysteamine Mean ± SD*		*n*	*Control Mean ± SD*		*n*
		pre	*post*		*pre*	*post*	
1	Nguyen *et al.* 2020	7,1 ± 3,4	5.6 ± 2.73	10	9,2 ± 5,7	6.29 ± 4.8	10
2	Lima *et al.* 2020	9,0±1,72	5,53±1,16	20	5,74±1,44	2±0,57	20
3	Sepaskhah *et al.* 2022	6,69±2,96	4.47 ± 2.16	31	6,26±3,25	3.87 ± 2.00	34

Overall the combination for topical cysteamine effectiveness compared with hydroquinone with or other additions in week 8 showed the overall standardized mean difference mMASI score was 0.33 with a CI of 95%, -0.02 to 0.68. This showed that there was a greater decrease in mMASI scores in the control group than the cysteamine group but the difference was statistically insignificant (p=0.07).

Based on the data in **Table 3**, the research of Nguyen *et al.* showed a decrease in mMASI scores in the cysteamine group and control group. The mMASI score in the cysteamine group before treatment was 9.0±1.72 and after treatment was 5.6±2.73, while the mMASI score in the control group before treatment was 9.2±5.7 and after treatment was 6.29±4.8. Lima *et al.*'s research, showed a decrease in mMASI scores in both groups with mMASI scores before treatment in the cysteamine group was 9.0±1.72 and after treatment decreased to 5.53±1.16, while the mMASI score before treatment in the control group was 5.74±1.44 and after treatment decreased to 2±0.57. In the study of Sepaskhah *et al.* also showed a decrease in both groups, with the mMASI score before treatment in the cysteamine group was 6.69±2.96 and after treatment decreased to 4.47±2.16, while the mMASI score before treatment in the control group was 6.26±3.25 and after treatment decreased to 3.87±2.

The results of the meta-analysis of the effectiveness of topical cystamine compared to control after treatment at week 16 in melasma patients can be seen in **Figure 3**.

Figure 3 shows the results of a metaanalysis of the effectiveness of topical cystamine compared to a control to the mMASI score of melasma patients at week 16. Metaanalysis showed that heterogeneity tests comparing topical and control overall were insignificant (p=0.89) with a value of I^2=0%, indicating that the research data used for metaanalysis were homogeneous. Based on this, a fixed-effect model is used in calculating metaanalysis.

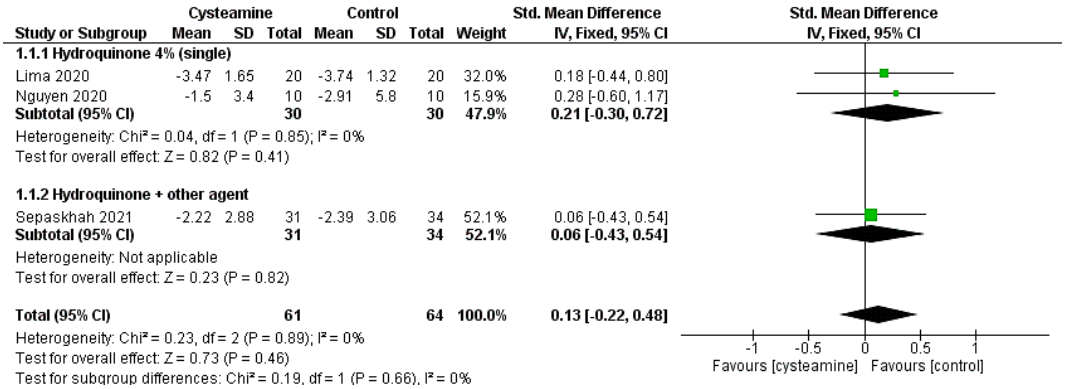

Figure 3 Results of a meta-analysis of the effectiveness of topical cysteamine compared with control to mMASI scores at week 16 in melasma patients

Table 4 Differences in mean MELASQoL scores in cysteamine and control groups.

No	*Study*	*Cysteamine*		*n*	*Control*		*n*
		Mean ± SD			*Mean ± SD*		
		pre	*post*		*pre*	*post*	
1	Lima *et al.* 2020	53,9±4,33	43,54±7,92	20	44,48±4,02	29,79±8,32	20
2	Sepaskhah *et al.* 2022	42.90 ± 18.05	34.96 ± 18.56	31	41.55 ± 16.84	33,32 ± 16,60	34

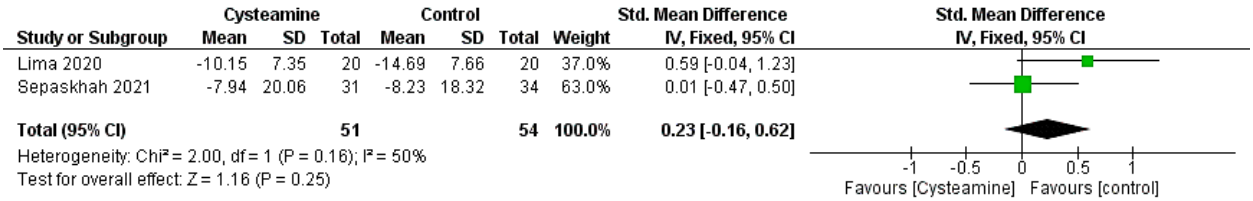

Figure 4 Results of a meta-analysis of the effectiveness of topical cysteamine compared with control to MELASQoL scores in melasma patients.

The results of a meta-analysis comparing topical cysteamine with 4% topical hydroquinone showed the overall standardized mean difference value of the mMASI score was 0.06 with a CI of 95%, -0.43 to 0.54. This showed that there was a greater decrease in mMASI scores in the control group than in the cysteamine group but the difference was statistically insignificant (p=0.41). The results of a meta-analysis comparing topical cysteamine and 4% topical hydroquinone with other additions showed the overall standardized mean difference value of the mMASI score was 0.30 with a CI of 95%, -0.19 to 0.79. This showed that there was a greater decrease in mMASI scores in the control group than the cysteamine group but the difference was statistically insignificant (p=0.82).

Overall, the combination for topical cysteamine effectiveness compared with control in week 16 showed the overall standardized mean difference mMASI score was 0.13 with a CI of 95%, -0.22 to 0.48. This showed that there was a greater decrease in mMASI scores in the control group than the cysteamine group but the difference was statistically insignificant (p=0.46).

2. Results of Meta-analysis of Topical Cysteamine Effectiveness Based on MELASQoL Score

Differences in mean MELASQoL scores before and after in the treatment group that got topical cysteamine and the control group in week 16 are shown in **Table 4**.

Based on the data in **Table 4**, the research of Lima *et al.* showed a decrease in MELASQoL scores in the cysteamine group and the control group. The MELASQoL score in the cysteamine group before treatment was 53.90±4.33 and after treatment it decreased to 43.54±7.92, while the MELASQoL score in the control group before treatment was 44.48±4.02 and decreased after treatment to 29.79±8.32. Research by Sepaskhah *et al.* also showed a decrease in MELASQoL scores in both groups, with the MELASQoL score before treatment being 44.48±4.02 and decreasing after treatment to 33.32±16.60.

The results of the metaanalysis of the effectiveness of topical cystamine compared to the control to the MELASQoL score after treatment at week 16 in melasma patients can be seen in **Figure 4**.

Figure 4 shows the results of a meta-analysis of the effectiveness of topical cystamine compared to control to the MELASQoL score in week 16 of melasma patients. The meta-analysis showed that heterogeneity assays comparing topical cystamine and hydroquinone as a whole were

Table 5 Risk of bias in studies used for systematic reviews and meta-analyses.

	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Bias	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	AHRQ Standard
Nguyen *et al.* (2020)	+	+	+	+	+	?	+	Good
Lima *et al.* (2020)	+	?	+	+	?	+	+	Good
Sepaskhah *et al.* (2022)	+	+	+	+	+	+	+	Good

Circle symbol of ● with a positive sign indicating a low risk of bias, circle symbol of ● with a question mark the risk of bias cannot be assessed, circle symbol of ● with a negative sign indicates a high risk of bias.

insignificant (p=0.16) with a value of I^2=50%, indicating that the research data used for meta-analysis were homogeneous. Based on this, meta-analysis is carried out using a fixed-effect model.

The results of the meta-analysis comparing the topical cysteamine group with the control group showed that the overall standardized mean difference score of MELASQoL was 0.23 with a CI of 95%, -0.16 to 0.62. This showed that there was a greater decrease in MELASQoL scores in the control group than the cysteamine group but the difference was statistically insignificant (p=0.25).

Risk of Bias in Included Studies

The risk of bias from the studies included in the analysis, both qualitatively and quantitatively assessed using The Cochrane Collecting data – form for RCTs only and The Cochrane Collaboration's tool for assessing risk of bias in randomized trials, includes randomization, allocation concealment, blinding of research subjects, blinding outcomes, incomplete outcome data, selection of reported outcomes, and other biases.

In **Table 5** there are three articles included in the meta-analysis. It shows the research of Nguyen *et al.* 2020; Lima *et al.* 2020; and Sepaskhah *et al.* 2022 has a low risk of bias. The research of Nguyen *et al.* 2020 is a double-blind RCT study. Randomization was carried out with computer generated randomization, concealment and blinding have also been reported, but blinding in officers who observed outcomes on the study subjects was not clearly reported. Overall the research of Nguyen *et al.* 2020 had a low risk of bias. Research Lima *et al.* was also a clinical trial but was not mentioned as a double blind RCT. This study is a quasi-randomized clinical trial, therefore it is not possible to do blinding on drugs given to patients, but blinding is done on evaluators. Researchers have also made efforts to minimize bias so that overall research by Lima *et al.* has a low risk of bias. The Sepaskhah *et al.* research is an RCT study. Randomization is done by permuted block randomization, in individual units, using random allocation software. Blinding in this study could not be done because of differences in the way of use in treatment, but data collectors and outcome assessors did not know the treatment each patient received. Overall the research of Sepaskhah *et al.* has a low risk of bias.

The entire study, each of which has been converted according to Agency for Healthcare Research and Quality (AHRQ) standards, shows that the 3 RCTs included in this study have a "Good" quality.

Discussion

This study is a meta-analytical observational study, systematic review and meta-analysis of the effectiveness of cysteamine as a depigmentation agent in melasma patients with mMASI score and MELASQoL score parameters. Melasma is a disorder of hypermelanosis characterized by the presence of a light brown to dark brown macula in the face and neck area. The pathogenesis of melasma is quite complex, not yet known for certain and is related to several causative factors including UV lighst, hormonal changes and genetic predisposition.[28] UV lights are known to stimulate the proliferation and migration of melanocytes as well as trigger various cytokines in keratinocytes that play a role in the formation of melanin.[29,30] Melasma lesions have a higher expression of estrogen receptors compared to the surrounding normal skin. The bonding of estradiol with estrogen receptors causes increased expression of melanocortin-1 receptors (MCR1) in melanocytes, triggering the melanogenesis process.[31] Estrogen will also trigger melanogenesis through activation of the cAMP-PKA pathway because estrogen will increase cAMP levels and inhibit PKA pathways thereby activating the tyrosinase enzyme. Genetic factors involve the migration of melanoblasts and their development and differentiation in the skin where the morphology of melanocytes, the matrix structure of melanosomes, tyrosinase activity and the type of melanin synthesized are all under genetic control. Melanocortin 1 Receptor (MCIR) gene plays a role in skin pigmentation.[32,33]

The current therapies for treating melasma are quite diverse, but there is no single definitive therapy that has been shown to be effective for melasma. The chronic and frequently relapsing nature of melasma makes it a challenge in determining the right therapy and treatment. Hydroquinone (HQ) has often been used as a first-line therapy for melasma therapy since more than 60 years ago.[2,16,19,34] This depigmentation agent works by inhibiting the enzyme tyrosinase which will reduce pigment production. Hydroquinone also has a cytotoxic effect not only against melanocytes but also other cells such as epidermal cells, for example keratinocytes. In long-term use it can trigger the onset of exogenous oochronosis. This disorder can occur in individuals who use HQ in the long term and are exposed to sunlight by being marked on darker areas of the face smeared with HQ. Some studies have shown that hydroquinone also induces mutations in ovarian cells in Chinese hamster V79. But to date there has been no reported malignancy or skin cancer correlated with topical use of hydroquinone on human skin. Despite this, topical hydroquinone as a depigmentation agent is prohibited from its use in some countries. Other side effects that have been reported are irritant contact dermatitis, itchy sensation, erythema, as well as xerosis.[35,36]

The search for new, safer depigmentation agents continues. Currently, many studies are carried out, one of which is on cysteamine. Cysteamine is a simple aminothiol that can be found evenly distributed throughout mammalian tissue and is most commonly found in mammalian milk. In milk, cysteamine acts as an antioxidant and plays a protective role as an antitumor, anti-carcinogenic and anti-mutagenic agent. Cysteamine also acts as a radio protector that protects cells from mutagenic and lethal effects due to ion radiation by eating free radicals directly.[37,38]

It started from the research of Chavin *et al.* 1960 who injected cysteamine into the skin of black goldfish. In this study, the cysteamine molecule was known to induce digestion in local and systemic melanin synthesis (melanophore and melanocyte lysis).[22] Furthermore, Hsu *et al.* examined cystamine applied to the ears of black female guinea pigs. Evaluation with a dermatoscope, chromameter and histopathological examination gave a fairly strong picture of the depigmentation effect.[39] Research continued on the administration of cystamine on the skin of black guinea pigs which gave the result that melanocytes were specific targets of cysteamine because there was a decrease in the number of epidermal melanocytes.[40] Subsequent studies were conducted by Qiu *et al.* who reported that cysteamine depigmentation played a role through its interaction with products catalyzed by the enzyme tyrosinase (the result of isolated oxidation of DOPA) which inhibits pigment synthesis. The study confirmed that the mechanism of cystamine is an inhibition of melanogenesis and not melanocytotoxicity as in hydroquinone.[41]

Research on cystamine as a topical depigmentation agent was constrained because the sulfur smell caused was quite pungent, but over time the problem could be treated and randomized trials of cysteamine against placebo began to be carried out by Mansouri *et al.* 2015 which was then continued by Farshi *et al.* 2018. The results of the two studies stated that cysteamine was able to lower MASI scores lower than placebo and statistically significant.[10,21]

The systematic review conducted on the 3 studies gave the results, that there was a decrease in the severity of melasma in both groups based on mMASI scores with the results of a systematic review of the three studies in which the overall study obtained a decrease in mMASI scores. There was also an improvement in the quality of life in both groups based on the MELASQoL score, this is in accordance with the results of a systematic review of the three studies which gave the results of a decrease in MELASQoL scores in both groups.

Metaanalysis was also carried out on these three studies. In a study to evaluate the effectiveness of cysteamine as a depigmentation agent towards mMASI scores, quantitative data analysis provided significant results between baseline and observation results in weeks 8 and 16 in both research groups. The decline in mMASI scores was seen in the evaluation in week 8 which continued to increase in the evaluation week 16. This indicates that cysteamine is well tolerated and when used consistently can provide a greater depigmentation effect. The decrease in mMASI score was also between the two groups where the decrease occurred more in the control group, but after analysis the difference was not statistically significant ($p=0.92$ and $p=0.89$). This insignificant difference indicates that cysteamine has the ability as a depigmentation agent that almost resembles that of a control group.

Meta-analysis was also carried out on the quality of life of patients using the MELASQoL (Melasma Quality of Life) score parameter. Metaanalysis of this study resulted in a significant decrease in MELASQoL scores between the baseline and the evaluation carried out at week 16. A decrease in MELASQoL scores indicates that the cysteamine used consistently can help improve the quality of life of patients characterized by a decrease in MELASQoL scores at week 16 compared to the baseline. The decline in MELASQoL scores occurred in both groups where a larger decrease was seen in the control group, but quantitative

analysis showed that the differences were not statistically significant (p=0.92 and p=0.89). This insignificant difference indicates that cystamine can improve the quality of life of sufferers, which is similar to the ability of hydroquinone to improve the quality of life of patients.

The side effects reported from all three studies varied. Research by Nguyen *et al.* gave the results of the cysteamine group experiencing more side effects such as erythema, irritation, warmth, pruritus. While in the hydroquinone group it gives side effects such as erythema and dry taste. This is likely because the study was conducted in the summer in Australia that increased skin irritation and erythema.[26] Research Lima *et al.* reported side effects occurring in the cysteamine group of about 20% of the subjects and side effects including erythema, desquamation and warm sensations did not differ statistically significantly when compared to the control group (P> 0.17).[27] The study of Sepaskhah *et al.* reported that 10 patients out of 76 patients experienced side effects, including erythema, warm sensations, pruritus to moderate erythema and itching leading to allergic contact dermatitis which caused 3 patients discontinue therapy. While from the hydroquinone group there were 4 patients with mild pruritus, blackheads, photosensitivity and dry lips. These side effects are temporary which may improve after treatment is discontinued. In other studies, it was also reported that there was a slight discomfort due to the sulfur-like smell produced by cysteamine, but generally patients were still able to tolerate it. Currently the formulation of cysteamine continues to develop so that it can be accepted by the public better.

The results of the meta-analysis suggest that cysteamine can be an alternative therapy in the treatment of melasma because it acts as a depigmentation agent capable of providing hydroquinone-like results but with milder and reversible side effects when compared to hydroquinone as a first-line therapy.

Future research related to cysteamine needs to be studied more regarding the ability of cysteamine in recalcitrant cases. Kasraee *et al.* reported the ability of cysteamine to provide significant results in overcoming recalcitrant cases, where previously resistant to Kligman's formula then showed improvement after using cysteamine for 4 months, and after using twice a week for three years still showed stable results in the absence of side effects.[42] Mathe *et al.* also reported a woman with Recalcitrant Post-Inflammatory Hyperpigmentation (HPI) against the cream a Kligman modification that provided an improved response after using cysteamine for 4 months without any side effects.[43]

The limitation of this study is that the number of samples from the RCTs involved is quite small. In the future, it is necessary to conduct various RCT studies on cystamine involving larger subjects. The existence of restrictions on inclusion criteria in this study using hydroquinone control with or without other additions, can be a barrier that reduces the data for analysis so that the number of subjects that can be involved in this study is limited. In addition, the research time conducted for treatment only used a period of 4 months. The authors expect future research with longer research time and more subjects involved to see better about the effectiveness of long-term therapy and the side effects that may arise during treatment.

Conclusion

According to the results of the systematic review and meta-analysis carried out, it can be concluded that topical cystamine is effective as a

depigmentation agent in lowering the severity of melasma and improving the quality of life of patients.

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