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ORIGINAL RESEARCH

Evaluation of the efficacy of cysteamine cream compared to hydroquinone in the treatment of melasma: A randomised, double-blinded trial

Jennifer Nguyen[1] | Laura Remyn[2] | In Young Chung[3] | Anthony Honigman[4] | Shima Gourani-Tehrani[5] | Ilycia Wutami[2] | Celestine Wong[5,6] | Eldho Paul[7] | Michelle Rodrigues[5,8]

[1]Victorian Melanoma Service, Alfred Health, Melbourne, [2]Faculty of Medicine, Dentistry and Health Sciences, Melbourne University, Parkville, [3]The Royal Victorian Eye and Ear Hospital, East Melbourne, [4]St Vincent's Hospital, Fitzroy, [5]Chroma Dermatology, Pigment and Skin of Colour Centre, Wheelers Hill, [6]Department of Dermatology, Monash Health, Clayton, [7]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, and [8]Department of Dermatology and Department of Paediatrics, Royal Children's Hospital & Melbourne University, Melbourne, Victoria, Australia

ABSTRACT

Background/Objective: Melasma is a commonly acquired disorder of hyperpigmentation that often poses a therapeutic challenge for dermatologists. Recently, cysteamine cream has shown promising results compared to placebo. This study aims to determine the efficacy of cysteamine cream compared to hydroquinone cream in the treatment of melasma.

Methods: A randomised, double-blinded, single-centre trial was conducted in Victoria, Australia. 20 recruited participants were given either cysteamine cream or hydroquinone cream for 16 weeks. The primary outcome measure was a change in the modified Melasma Area and Severity Index (mMASI). Quality of life at baseline and week 16 as well as standard digital photography at each follow-up visit was assessed as secondary outcome measures.

Results: At week 16, 14 participants completed the study with 5 participants in the cysteamine group and 9 patients in the hydroquinone group. In the intention to treat analysis, there was a 1.52 ± 0.69 (21.3%) reduction in mMASI for the cysteamine group and a 2.96 ± 1.15 (32%) reduction in the hydroquinone group. The difference between groups was not statistically significant ($P = 0.3$). Hydroquinone cream was generally better tolerated that cysteamine cream.

Conclusion: Our study suggests that topical cysteamine may have comparable efficacy to topical hydroquinone. Cysteamine thus provides a possible alternative to patients and clinicians who wish to avoid or rotate off topical hydroquinone. While side effects were more common for participants using cysteamine compared with hydroquinone, these were mild and reversible. Larger studies comparing cysteamine and hydroquinone are required to support these findings.

Key words: cysteamine, hydroquinone, melasma, mMASI, randomised controlled trial, topical.

INTRODUCTION

Melasma is a multifaceted condition characterised by prominent brown hyperpigmented macules or patches.[1] Melasma occurs on sun-exposed areas and is more likely to affect females of childbearing age with Fitzpatrick skin

Correspondence: Jennifer Nguyen, Victorian Melanoma Service, Alfred Health, Melbourne, Victoria. Email: jennifer.n@hotmail.com

Site of research conduction: Chroma Dermatology, Pigment and Skin of Colour Centre, Ground Floor, Suite 15/202 Jells Rd, Wheelers Hill, Victoria 3150.

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Jennifer Nguyen, MBBS (Hons). Laura Remyn, MD, BBiomed. In Young Chung, MBBS (Hons), BBMed. Anthony Honigman, MBBS (Hons). Shima Gourani-Tehrani, BDermSci. Ilycia Wutami, BBmed. Celestine Wong, MBBS, BMedSci, FACD, Eldho Paul, PhD. Michelle Rodrigues, MBBS (Hons), FACD.

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prototype III and IV.[1] Although considered to be a benign condition, the cosmetic appearance of melasma can cause significant psychological morbidity.[1]

The current first-line topical treatment for melasma is hydroquinone which has demonstrated both efficacy and tolerability.[2-8] Other treatment options used for melasma include topical retinoids, tranexamic acid, azelaic acid, alpha-hydroxy acids, ascorbic acid and corticosteroids. When used as monotherapy, these agents have generally only demonstrated minimal lightening effects, though combination therapy has been more successful.[3-8]

Cysteamine hydrochloride is a molecule that exhibits potent depigmenting properties. It has been shown to be a promising agent for the treatment of hyperpigmentation.[9-11] Recently, two randomised placebo blind controlled studies were conducted with both demonstrating very favourable results for the use of topical cysteamine for melasma.[12,13]

We performed a randomised controlled study which comparing the effects of topical cysteamine to current first-line therapy, topical hydroquinone in the management of melasma.

MATERIALS AND METHODS

A randomised controlled, double-blinded study was conducted at Chroma Dermatology, Pigment and Skin of Colour Centre in Wheelers Hill, Melbourne, Australia. This study received ethics approval from Bellberry Private Limited. All participants provided written informed consent prior to commencing the study. Participants were prospectively recruited from Chroma Dermatology. Female participants aged 18 years and over with at least 3 months history of melasma were included in the study. The severity of melasma was determined by the modified Melasma Area and Severity Index (mMASI). Mild, moderate and severe melasma was defined as a mMASI of 2.7–5.7, 5.8–7.9 and ≥8, respectively.[14]

The exclusion criteria included (i) pregnancy and lactation breastfeeding, (ii) rashes on face, (iii) significant sun exposure (from occupation with more than two hours per day of outdoor work), (iv) use of topical hydroquinone, (v) bleaching agents, (vi) topical steroids, (vii) topical retinoic acid or (viii) laser therapy to the face in the past month.

Overview of the study is shown in Figure S1.

Eligible participants were randomised to receive either cysteamine cream or hydroquinone cream in a 1:1 ratio. Computer generated randomisation was performed by a study pharmacist from Scientis Pharma, Geneva, Switzerland. The blinding process was ensured through labelling of study creams with protocol number, expiry date and randomisation code.

Cysteamine cream is recommended to be applied to the skin and then washed off after 15 min, whereas hydroquinone cream is recommended to remain on the skin after application. To ensure adequate blinding of the study creams, each participant was provided with two study medication tubes labelled as 'first' and 'second' cream. For the cysteamine group, the 'first' cream contained cysteamine 5% and the second cream contained vehicle ingredients of hydroquinone cream (without active hydroquinone). For the hydroquinone group, the 'first' cream contained vehicle ingredients of cysteamine cream (without active cysteamine), and the 'second cream' contained hydroquinone 4%. Participants were advised to apply a thin layer of the 'first' cream to affected areas and leave for 15 min before washing it off and then apply the 'second' cream daily in the morning or evening, before a shower. Cysteamine cream is known to have a very offensive odour but the new formula of this, which was used in this study, has a significant reduction in odour.[12,13]

Participants were also provided with sunscreen (Avène Eau Thermale® sun protection factor 50+ face and body lotion) and were instructed to apply regularly to the face 15 min prior to sun exposure and reapplied immediately after 40 min of swimming or sweating or otherwise reapplied 2 hourly. Patients were advised to apply the cream daily for a total treatment period of 16 weeks. Avoidance of sun exposure and any facial treatment or laser therapy was also advised. Furthermore, all instructions were provided to participants in a written document.

At baseline, medical history, concomitant medication, facial examination, mMASI, clinical photography and quality of life (QoL) were assessed. At weeks 2 and 4, a phone call was conducted to assess the patients' treatment compliance and development of any adverse events.

An in-person study visit was conducted at weeks 8 and 16, where all participants were reviewed for compliance, adverse events, facial examination, mMASI and clinical photography. QoL was also assessed at the final week 16 study visit.

Statistical analysis

We expected a 30–40% change in mMASI in the hydroquinone group and a 60–80% change in the cysteamine group. Using the expected proportional change of 60% for cysteamine (48.5 to 19.4 = 29.1) and 30% for hydroquinone (48.5 to 34 = 14.5), a mean difference of 14.5 with a standard deviation (SD) of 16.4 was estimated. To show this difference between groups with 80% power at the 5% level of significance using an unpaired *t*-test, a total sample size of 40 participants was required. A multi-centre study with the recruitment of 20 patients at each site was planned. However, due to problematic logistics and country regulations around hydroquinone use, other international sites were not able to participate the study. As a result, 20 patients were recruited from one participating site.

The primary outcome was change in mMASI score from baseline to weeks 8 and 16. The effectiveness analysis was performed according to the intention to treat principle. Per protocol analysis was also conducted to determine effectiveness within participants who completed the intervention. Comparisons between groups were made using Student *t*-tests, chi-square or Fisher exact test with results reported as mean differences and standard deviations (SD) or numbers and percentages. A two-sided *P* value of 0.05 was considered statistically significant. All analyses were

performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

The study was conducted between May 2019 and March 2020. 24 females were pre-screened via telephone, and all met the inclusion and exclusion criteria. 2 participants decided not to be part of the in-person screening, and 2 participants were omitted due to supply constraints on the creams. From these participants, 20 participants attended the in-person screening and were eligible for the study (Figure S1). 10 participants were randomised into the cysteamine treatment group, and 10 participants were randomised to the hydroquinone group.

The baseline characteristics collected included age, duration, type and severity of melasma, Fitzpatrick skin type, family history and mMASI scores, and were similar between the hydroquinone and cysteamine groups as shown in Table 1. The hydroquinone group, however, had a higher baseline quality of life score of 47.3 ± 14.9 compared to the cysteamine group 34.8 ± 11.5 ($P = 0.045$).

For the cysteamine group, one participant left the study due to acne breakout prior to the 8-week study visit. Between the 8-week and 16-week study visit, one participant left due to no improvement and one participant was lost to follow-up. It is also noted, two participants in the cysteamine group did not follow the protocol with regards to regular cream application. One participant applied the cysteamine cream twice a week from week 9 onwards due to irritation and burning. The other participant was not able to apply the cream daily due to her personal schedule. For the hydroquinone group, One participant was excluded from the study before the 8-week visit as the patient had self-reduced the study cream and sunscreen application to her cheeks to 2–3 days per week due to skin irritation, dryness, erythema, pruritus and rosacea flare.

Both intention to treat analysis (cysteamine $n = 10$, hydroquinone $n = 10$) and per protocol analysis (cysteamine $n = 5$, hydroquinone $n = 9$) were conducted. Results of the mMASI are summarised in Table 2. Figure 1 and Figure 2 demonstrate an example of a patient with severe melasma who experienced clinical improvement of her melasma from baseline compared to after 16 weeks of cysteamine treatment.

Table 1 Baseline characteristics

Patient characteristic	Hydroquinone ($n = 10$)	Cysteamine ($n = 10$)	*P*-value
Age, mean ± SD	44.2 ± 7.3	43.1 ± 9.2	0.77
Skin Type, *n* (%)			
II	3 (30%)	2 (20%)	0.59
III	4 (40%)	6 (60%)	
IV	3 (30%)	1 (10%)	
V	0 (0)	1 (10%)	
Melasma type, *n* (%)			
Deep	9 (90%)	8 (80%)	1.0
Epidermal	1 (10%)	1 (10%)	
Mixed	0 (0)	1 (10%)	
Duration of melasma (years), median (IQR)	7 (2–10)	5.5 (3–18)	0.88
Family history of melasma, *n* (%)	4 (40)	6 (60)	0.37
mMASI score, mean ± SD	9.2 ± 5.7	7.1 ± 3.4	0.32
QoL score, mean ± SD	47.3 ± 14.9	34.8 ± 11.5	0.05

Baseline mean mMASI for the cysteamine and the hydroquinone group was 7.1 ± 3.41 and 9.2 ± 5.7, respectively. Using intention to treat analysis, at week 8, the mean mMASI for cysteamine and hydroquinone groups had reduced to 6.0 ± 2.2 (15.7% reduction) and 5.7 ± 4.2 (37.9% reduction), respectively. At week 16, the mean mMASI for the cysteamine group had further reduced to 5.6 ± 2.7 (21.3% reduction from baseline) and had remained relatively consistent in the hydroquinone group at 6.3 ± 4.8 (32% reduction from baseline). The difference in reduction between the two groups was not statistically significant at week 8 and week 16. In the per protocol analysis, there was a larger difference in cysteamine group from baseline to week 16 of 3.1 ± 1.9 (39.1%) compared to the intention to treat analysis. For all other results, the intention to treat and per protocol analysis were similar.

Table 2 mMASI scores

	Baseline	8 weeks	16 weeks
Intention to treat analysis[a]			
Hydroquinone (n = 10)	9.2 ± 5.7	5.7 ± 4.2	6.29 ± 4.8
Cysteamine($n = 10$)	7.1 ± 3.4	6.0 ± 2.2	5.60 ± 2.73
Difference from baseline hydroquinone		3.5 ± 3.7 (37.9%)	23.0 ± 1.1 (32%)
Difference from baseline cysteamine		1.1 ± 1.5 (15.7%)	1.5 ± 0.69 (21.3%)
Between group difference, *P*-value		*P = 0.07*	*P = 0.30*
Per protocol analysis[b]			
Hydroquinone ($n = 9$)	9.8 ± 5.8	5.9 ± 4.4	6.5 ± 5.0
Cysteamine ($n = 5$)	8.0 ± 4.4	6.4 ± 2.7	4.9 ± 2.7
Difference from baseline hydroquinone		3.8 ± 3.7 (39.2%)	3.2 ± 3.7 (33%)
Difference from baseline cysteamine		1.6 ± 1.9 (19.7%)	3.1 ± 1.9 (39.1%)
Between group difference, *P*-value		$P = 0.24$	$P = 0.96$

[a]Intention to treat analysis: all randomised participants were included.
[b]Per protocol analysis: participants non compliant to protocol were excluded.

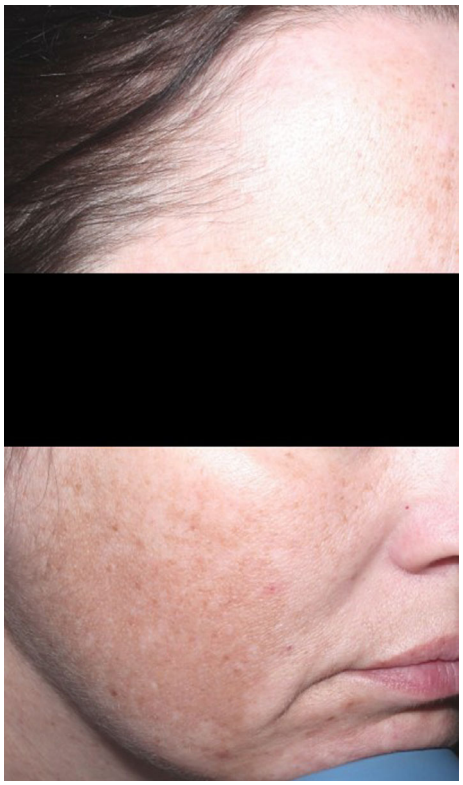

Figure 1 Baseline image of a participant with severe melasma with hyperpigmentation of the right cheek.

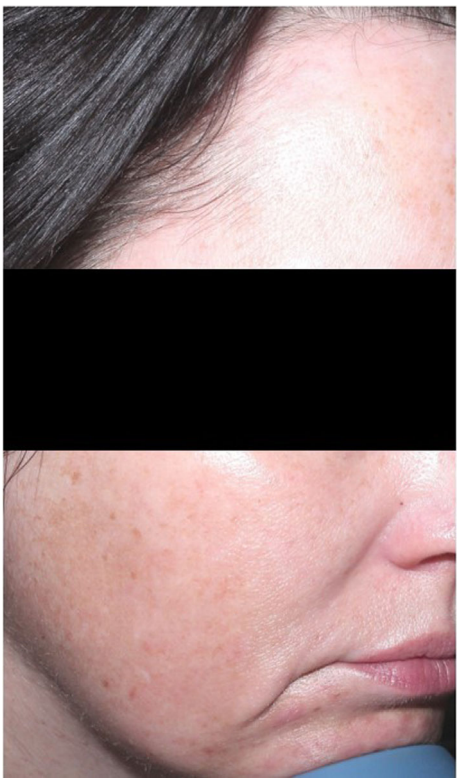

Figure 2 Same participant from Figure 1, after 16 weeks of cysteamine cream treatment showing improved hyperpigmentation of the right cheek.

There was a small improvement in QoL scores for both cysteamine and hydroquinone groups following 16 weeks of treatment as shown in Table 3. The results however were not statistically significantly and both intention to treat analysis and per protocol yielded similar differences.

Table 3 QoL scores at 16 weeks

	Hydroquinone	Cysteamine	*P* value
Intention to treat analysis			
Change from baseline	3.9 ± 13.1	1.1 ± 3.4	0.52
Hydroquinone (n = 10)			
Cysteamine (n = 10)			
Per protocol analysis			
Change from baseline	4.3 ± 13.8	1.4 ± 5.0	0.66
Hydroquinone (n = 9)			
Cysteamine (n = 5)			

Side effects

From the cysteamine group, two participants experienced no side effects. two participants experienced redness and irritation of the skin shortly after applying the cream. One of these participants used the 'first' cream with active cysteamine twice a week at week 9 onwards due to side effects (which resolved after changing to this regime). One participant left the study before week 8 following having an acne breakout. The remaining six patients experienced either mild to moderate irritation, burning, pruritus or erythema shortly after applying the cream. One participant had commented on strange odour of the cream but overall, was not bothered by the smell and continued application for the duration of the study.

From the hydroquinone group, four participants experienced no side effects. one participant had reduced usage of the cream due to moderate irritation, dryness, redness and itch as well as a flare-up of rosacea and consequently left the trial after 8 weeks. This participant has a background history of rosacea and reported previous similar rosacea flares with sunscreen application. On self-reducing study cream and sunscreen application to 2–3 days per week for the cheeks, she reported improvement of symptoms. She continued to regularly apply the study cream and sunscreen application to the forehead and chin with no significant side effects. The remaining five participants experienced mild redness or dryness shortly after applying.

DISCUSSION

Despite the plethora of treatment options available for melasma, there is no definitive topical, oral or light-based treatment option which assures improvement.[3-8] The chronic and relapsing nature of melasma makes the condition notoriously challenging to treat and maintain.

Currently, the most extensively studied and first-line management option is topical hydroquinone which has been used for over 60 years as a de-pigmenting agent.[3-8] Hydroquinone is a tyrosinase inhibitor which is a rate-limiting step for pigment production and may be melanocytoxic.[15,16] Topical hydroquinone is generally well tolerated with mild to moderate side effects which most commonly include irritant and allergic contact dermatitis.[3-8] In rare cases, ochronosis can occur with long-term use of hydroquinone and inadequate sun protection. There have been no cases of malignancies or skin cancer related to topical application of hydroquinone in humans. Despite this, topical hydroquinone has been banned by several drug regulatory authorities around the world as a cosmetic depigmenting agent. In Australia, topical hydroquinone is used as an off-label treatment for melasma and requires a doctor's prescription when concentrations of above 2% are required.

In search for new novel agents, topical cysteamine, a non-melanocytoxic, non-mutagenic molecule known to produce depigmentation by inhibiting melanogenesis was considered.[9,10] Despite having been discovered decades ago, the strong offensive odour of cysteamine prohibited its use as a topical depigmenting agent.[9-13] Recently, means to reduce the odour from cysteamine was achieved and this was followed up by two randomised placebo-controlled trials.[12,13] Both of these trials were conducted at the same institution showing promising results for cysteamine in the treatment of melasma.[12] The first study compared cysteamine cream and placebo with 25 participants in each study arm. There was a significant mean reduction of melasma measured by the MASI of 65.1% compared to 11.2% in the placebo group following 16 weeks of use.[12]

The second study was conducted similarly with 20 participants in both the cysteamine and placebo arms.[13] Again, a significant mean reduction of melasma measured by the MASI of 62% in the cysteamine group compared to 22% in the placebo group. The second study also utilised a novel scoring system known as the Dermacatch score which portrayed similar results. Cysteamine was generally well tolerated in both studies with only a small proportion of participants reporting mild to moderate side effects which included erythema, dryness, itching, burning and/or irritation. In the first trial, some participants commented about the cysteamine odour but could tolerate it with no concerns. The reduction seen in the placebo group could be explained by concomitant use of regular sunscreen which is mandatory baseline management of melasma.

With promising results from these cysteamine trials, we conducted a randomised control trial comparing topical cysteamine to current first-line topical management melasma, hydroquinone. Our trial had similar baseline characteristics to the previous two studies though our study involved a more heterogeneous group including participants with Fitzpatrick skin type II. Additionally, rather than MASI, our study utilised the mMASI.[14] From the intention to treat analysis, the cysteamine group had a 21.3% reduction in mMASI and the hydroquinone group had a 32% reduction after 16 weeks which was a lower reduction comparable to previous studies.[12,13] We note that when per protocol analysis was used there was much larger effect of cysteamine at 16 weeks with a 39.1% reduction. This suggests that when cysteamine is well tolerated and used consistently its depigmenting effects are greater.

In contrast to the previous the cysteamine trials, 80% of our participants experienced side effects. These side effects ranged from significant erythema and irritation (which caused one participant to leave the study and the other to apply the cream twice a week) to mild and moderate irritation, burning, pruritus or erythema shortly after using the cream. Of note, this trial was undertaken during the spring and summer months in Melbourne, Australia, which could account for the increase in cutaneous irritation and erythema. Hydroquinone cream was generally well tolerated with only mild temporal erythema and dryness reported among the patients. However, there was one participant who exited the trial due to moderate irritation, dryness and pruritus. There were no significant changes in the QoL scores in both the cysteamine and hydroquinone group.

The main limitations of our study were the small sample size, which meant that the results were unfortunately not statistically significant. Additionally, although the cysteamine formulation used in this study had been prepared to have a reduced odour, the cream may have a remnant smell which could have impacted the blinding of the study. This is unlikely to be a significant factor as only one patient in the cysteamine group had commented on but was not bothered by the odour.

In our small randomised control study, we demonstrated that topical cysteamine may be as effective as topical hydroquinone after 16 weeks of application. Topical cysteamine may therefore play an important role as an non-hydroquinone topical agent for those with mild to moderate melasma. While side effects were more common for participants using cysteamine compared with hydroquinone, these effects were mild and reversible. Larger studies are required to make more conclusive evaluation of cysteamine's role in the therapeutic ladder for melasma.

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Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Figure S1. Study design.