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Original Article

Combination of 5% cysteamine serum and 3% tranexamic acid cream using layering technique for treatment of melasma: A pilot study

Anis Irawan Anwar[1], Reinecia Hidayat[1], Farida Tabri[1], Khairuddin Djawad[1], Andi Alfian Zainuddin[2], Suryani As'ad[3], Thomas Utomo[1], Wong Lip Wih[4], Jonathan Kurnia Wijaya[1]

[1] Department of Dermatology and Venereology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.
[2] Department of Public Health, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.
[3] Department of Clinical Nutrition, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia.
[4] Lipwih Synergylab Company, Indonesia.

Abstract

Objective To assess the effectiveness of 5% cysteamine serum combined with 3% tranexamic acid cream using layering technique for treatment of melasma.

Methods The study design is a pretest-posttest clinical trial conducted at the dermatology outpatient clinic of Hasanuddin University Hospital and Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia from December 2020-December 2021. A total of 40 subjects that met the inclusion criteria participated in the study. Subjects were instructed to cleanse their face at night and apply two drops of 5% cysteamine serum over the face for 15 minutes, followed with application of 1 fingertip unit (FTU) of 3% tranexamic acid cream. Parameters for assessment used in this study are modified melasma severity index (mMASI) score, pigmented facial spots using Janus Skin Analyzer®, L* value using Chromameter® and Melanin Index (MI) using Mexameter®.

Results There were significant improvements in all parameters with a mean mMASI score decrease of 0.42 point from 7.97 to 7.55 ($p < 0.05$), decreased pigmented facial spots from 52.29 to 49.17 ($p<0.05$), an increase of L* value from 46.82 to 50.88 from W0 to W8 using Chromameter® ($p<0.05$), and a 48.94-point decrease in MI using Mexameter ® from 359.49 to 310.55 ($p<0.05$).

Conclusion Combination of 5% cysteamine serum and 3% tranexamic acid cream using layering technique is a promising combined regiment for treatment of melasma.

Key words
Cysteamine Serum; Tranexamic Acid; Layering technique; Melasma.

Introduction

Melasma is a hyperpigmentation disorder characterized with hyperpigmented macules and patches with irregular borders.[1] The disorder is more prominent in people of color (Fitzpatrick III–V skin types), menopausal and pregnant women, and people with history of chronic and intense ultraviolet (UV) exposure. Lesions are usually symmetrical, appearing on sun-exposed areas of the face, such as the forehead, nose, cheeks and chin, malar and mandibular.[2]

The pathogenesis of melasma is complex and is yet to be fully understood, involving interactions between various internal and external factors, responsible for triggering lesions as well as

Address for correspondence
Dr. Anis Anwar
Department of Dermatology and Venereology, Faculty of Medicine, Hasanuddin University, Indonesia.
Email: anisianwar.md@gmail.com

recurrences. Although the condition is benign, the negative aesthetic implications of melasma can lead to significant morbidity that severely affect patient's quality of life (QoL).[3]

Although there are a wide array of treatment options available for melasma, management of the condition can be challenging, notably due to high rate of recurrences even after patients achieve complete resolution of lesions.[4] Topical treatments are considered to be the first-line treatment for melasma. The aims of melasma treatment are suppression of melanocyte proliferation, inhibition of melanosome formation and increasing melanosome degradation. In addition, the combination of several topical agents are reported to boost and compliment the efficacy therefore, providing better outcome with a high safety profile.[5]

Cysteamine hydrochloride (b-mercaptoethylamine hydrochloride) is an aminothiol compound with antioxidant and depigmenting properties. The substance has long been studied for the treatment of melasma.[6] At high concentrations, it is able to suppress the melanogenesis cascade through reduction of the tyrosinase enzyme activity, without being melanocytotoxic. However, this higher concentration is attributed to higher side-effects such as erythema and pain.[7,8]

Tranexamic acid (TA) has been widely recognized as a potent coagulant and depigmenting agent, and an alternative treatment of melasma. Various administration routes of TA are available, including intravenous, topical, and intradermal. The drug works by inhibiting plasmin activity through prevention of plasminogen adhesion to keratinocytes resulting in a decrease in prostaglandin that ultimately suppresses the melanocyte tyrosine kinase activity.[9]

The efficacy of topical TA has been reported in several studies showing significant improvements in modified melasma severity index (mMASI) score.[10,11] However, to our knowledge there are currently no studies that assess the efficacy of combined cysteamine and TA using layering technique for melasma. This paper explores the potential use of 5% cysteamine serum and 3% TA cream using layering technique for treatment of melasma.

Methods

This study is a pre-posttest clinical trial performed at the dermatology outpatient clinic at Wahidin Sudirohusodo Hospital and Hasanuddin Hospital, Makassar, South Sulawesi, Indonesia. between December 2020 - December 2021.

A total of 40 female subjects aged 31-54 years agreed to be part of the study. Subjects visited the dermatology outpatient clinic. The diagnosis of epidermal and mixed types melasma was made through history taking, physical examination, and wood lamp examination by a dermatologist. All subjects signed the informed consent form. Exclusion criteria included pregnancy, breastfeeding, menopause, undergoing hormonal treatment including contraception, suffering from any chronic inflammatory diseases, and history of consuming systemic tranexamic acid or antioxidants within the past three months prior to the start of the study.

On the initial visit (W0), the baseline mMASI score of subjects were determined, followed with measurements of mMASI score, facial spots using Janus Skin Analyzer®, L* value using Chromameter® and melanin index (MI) using Mexameter®. Subjects then were instructed to cleanse their face at night and apply two drops of 5% cysteamine serum over the face for 15 minutes, followed with application of one fingertip unit (FTU) of 3% tranexamic acid

cream over the face and cleansed the next morning. Biweekly evaluation was performed for eight weeks, with a total of five visits (W0, W2, W4, W6, W8), where evaluation of mMASI, facial spots, L* value and MI were performed.

mMASI Score The Melasma Area and Severity Index (MASI) was first proposed by Kimbrough-Green, *et al.* as an objective scoring system to determine severity of melasma. The modified MASI (mMASI) is an improvement of the MASI score and has long been used as an evaluation tool for the treatment of melasma.[12,13]

Janus Facial Analysis System® The Janus Facial Analysis System® (PSI, Korea), is a facial analysis device with a 10-megapixel ultra-high-resolution camera. Facial images are captured and analyzed with the built-in image analysis program. Facial spots indicate areas of hyperpigmentation on the epidermis, while UV Spots indicate areas of hyperpigmentation in the dermis.[14]

Chromameter® Chromameter® CR-400 (Konica Minolta, Japan) is an objective measuring tool for skin color with parameters of L*, a* and b* values through the reflection of a xenon lamp perpendicular to the probe at 450, 560, and 600nm. The L* value ranges from 0-100 and measures skin brightness (100 for white and 0 for black).[15,16]

Mexameter® Mexameter® MX18 (Courage and Khazaka, Germany) is a device that measure skin color through melanin and hemoglobin in the skin. It emits three specific wavelengths of light at 568nm, 660nm and 880nm, that are then reflected by the skin. The melanin index (MI) value is calculated from the intensity of light absorbed and reflected by melanin at 660nm (red light) and 880nm (infrared light) respectively. The erythema index (EI) is determined by the intensity of light absorbed and reflected by hemoglobin at 568nm (green light) and 660nm (red light) respectively.[15,16]

Statistical Analysis Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS. Inc.) using paired T-test and Wilcoxon test. A value is considered statistically significant if the p value is <0.05. Results are presented in the form of tables and graphs.

Results

Table 1 highlights the decrease in overall mMASI score between W0 and W8, with a mean decrease of 0.42 point during the duration of study from 7.97 to 7.55 ($p < 0.05$). Subsequently, consistent findings in the improvements in hyperpigmentation using the combination of 5% cysteamine serum and 3% TA were also highlighted at **Table 2** and **Figure 1**, as there was a decrease of facial spots with a 3.12-point decrease from a baseline score of 52.29 to 49.17 ($p<0.05$). Furthermore, evaluation of Chromameter® from **Table 3** and **Figure 2** revealed the baseline L* value at W0 of 46.82 that gradually and consistently increased to 50.88 at W8 ($p<0.05$). Lastly, evaluation in MI using Mexameter® at **Table 4** and **Figure 3** revealed a 48.94-point decrease in MI from a baseline

Table 1 mMASI Improvement (W0 and W8).

Week	*mMASI Score (Mean)*	*p-Value*
W0	7.97	0.025*
W8	7.55	

*Paired T-test.

Table 2 Stable Improvements in Facial Spots (W0 to W8).

Week	*Facial Spots (Mean)*	*p-Value*
W0	52.29	
W2	50.08	
W4	50.88	0.000*
W6	50.23	
W8	49.17	

*One Way ANOVA.

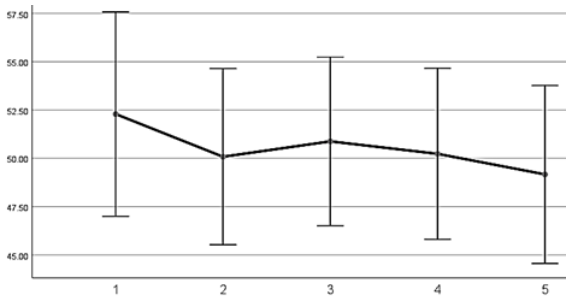

Figure 1 Overall Improvement in Facial Spots at W8.

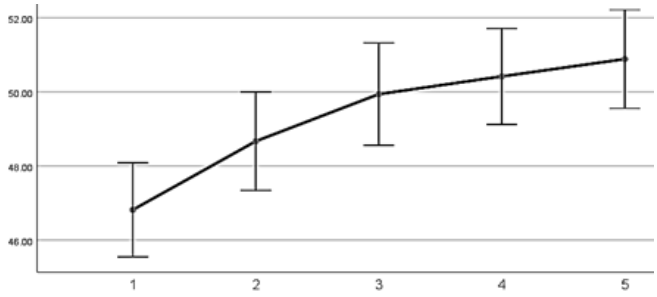

Figure 2 Changes in L* value.

Table 3 Improvements in L* Value (W0 to W8).

Week	*Facial Spots (Mean)*	*p-Value*
Week	L* Value (Mean)	
W0	46.82	
W2	48.67	0.000*
W4	49.94	
W6	50.42	
W8	50.88	

*One Way ANOVA.

Table 4 Improvement in Melanin Index (MI).

Week	*Melanin Index (Mean)*	*p-Value*
W0	359.49	
W2	334.28	
W4	323.22	0.000*
W6	310.26	
W8	310.55	

*One Way ANOVA.

value decrease in MI from a baseline value of 359.49 to 310.55 These changes are found to be consistent at each visit ($p<0.05$).

Discussion

Melasma is a chronic hyperpigmentation disorder that is challenging to treat due to its high recurrence rate and impact on the patient's QoL.[17] Although initially thought to only involve melanocytes, an increasing number of studies have shown a more nuanced pathogenesis of melasma, involving interactions of keratinocytes, mast cells, gene regulation disorders, increased vascularization, and disruption of the basement membrane.[18,19]

This study aimed to evaluate the efficacy of 5% cysteamine serum combined with 3% TA for treatment of melasma. Cysteamine and TA have each been described as topical options for treatment of melasma. Although in many studies hydroquinone (HQ) is considered to be the gold standard treatment for melasma, cysteamine is significantly less melanocytotoxic compared to HQ, providing a relatively superior safety profile.[7,20] The exact mechanism of action of cysteamine is yet to be fully understood. It is hypothesized that this thiol molecule acts through several different mechanisms, namely inhibition of the tyrosinase and peroxidase enzymes which are integral in the melanogenesis cascade and melanin synthesis by reducing the number of dopaquinone, binding of iron and copper ions, and increasing intracellular glutathione levels that acts as an intracellular regulator in melanin production.[21]

Previous studies have highlighted the effectiveness of 5% cysteamine for treatment of epidermal melasma, with significant reduction in mMASI score after 8 and 16 weeks of treatment compared to placebo.[7,8] Another study that compared cysteamine 5% with modified

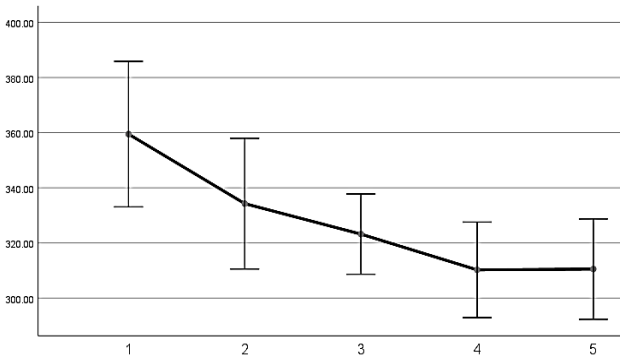

Figure 3 Changes in Melanin Index.

Kligman's formula for epidermal melasma demonstrated the superiority of cysteamine in reducing mMASI score with less apparent side effect.[21] However, conflicting results are reported regarding this matter, with other studies still consider HQ as more superior to cysteamine. Therefore further studies are needed.[6]

The combination with TA that works by inhibiting plasmin activity in keratinocytes aimed to prevent the binding of plasminogen to keratinocytes, leading to a decrease in prostaglandin production and further suppresses ion of melanogenesis. It has been suggested that plasmin plays an important role in angiogenesis, through conversion of the extracellular matrix of vascular endothelial growth factor (VEGF) into a free form, whereas tranexamic acid inhibits angiogenesis and also suppresses fibroblast growth factor (FGF)-induced neovascularization.[22]

Furthermore, TA has the ability to reverse melasma-related dermal changes such as increased vascularization.[3] One study that evaluated 3% TA compared to 3% HQ and 0.01% dexamethasone found a decreased mMASI score.[23] Another study demonstrated that topical TA also clinically improves melasma through a decrease in facial hypervascularization.[24] However, it should be noted that topical and intradermal administration of TA is still inferior compared to oral administration, as reported by a study by Khurana, *et al*.[10,12]

In our study, we found that the combination of 5% cysteamine and 3% TA was effective for treating both epidermal and mixed types of melasma. Several parameters that we assessed, including mMASI score, facial pigmented spots, L* value and MI have all shown consistent improvement after eight weeks of treatment. We opted using layering technique with cysteamine serum followed with TA cream to reduce the potential local side-effects such as inflammation, burning sensation and pruritus often associated with cysteamine use.[25]

To date, studies on cysteamine have been limited to treatment for epidermal melasma and there are still limited studies on its use for dermal melasma or recurrent cases of melasma.[26] MI is considered to be an objective parameter to measure melanin,[22] while an increase in the L* value indicates an increase in skin brightness.[16,27] Farshi, *et al*. through Mexameter, reported the effectiveness of 5% cysteamine in reducing MI in melasma patients.[7] In addition, comparative studies between topical 5% cysteamine and 4% hydroquinone did not result in significant differences, although both agents were able to show progressive depigmentation through colorimetric tests using Chromameter.[6] Karrabi, *et al.* conducted a study that aimed to compare the efficacy of 5% cysteamine cream with TA mesotherapy in melasma patients. The study revealed that both cysteamine and TA as measured using two parameters of mMASI and Dermacatch® (assessment of melanin content). The study revealed that both preparations provided similar results in depigmentation.[28]

To our knowledge this is the first study that evaluated the combination of cysteamine and TA using two different preparations and layering technique for melasma. As we found promising results, it is important that further research and evaluation preferably with a longer duration of study to be performed to completely establish its use for treatment of melasma.

Conclusion

The combination of 5% cysteamine serum and 3% tranexamic acid cream using layering

technique is a promising combined regiment for treatment of melasma.

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