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Original Article

The effectiveness of 1% cysteamine, 3% tranexamic acid, 2% galactomyces ferment filtrate and 4% niacinamide application using double layering technique as a brightening agent: Chromameter and Janus-III analysis

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Abstract

Introduction The combination of several topical agents with different vehicles or routes of administration is one of the therapeutic strategies that can be used to increase the effectiveness and possibly to reduce unwanted side-effects.

Objective To assess the efficacy of 1% cysteamine, 3% tranexamic acid, 2% galactomyces ferment filtrate, and 4% niacinamide as a facial brightening agent using the double layering technique of serum and cream.

Methods An open-label pre-post-test clinical trial was conducted for eight weeks using on 70 type-IV Fitzpatrick skin female participants between the ages of 31-50 years-old (mean age 37.8 years). Subjects were evaluated on a biweekly basis using chromameter and Janus-III Facial Analyzer.

Results At the end of the study there was a significant L* value increase from 52.10 at W0 to 56.40 at W4 (p=0.00) along with improvement on pigmented areas from 45.52 to 43.90 after eight weeks of treatment (p=0.00 and 0.01 respectively).

Conclusion Application of 1% cysteamine, 3% tranexamic acid, 2% galactomyces ferment filtrate and 4% niacinamide using double layering technique is a promising combination for facial brightness with notable reduced side-effects.

Key words
Cysteamine; Double layering; Skin brightness; Topical skin lightening agent.

Introduction

As we age, the skin experiences agings which manifests as hyperpigmentation and lacklustre skin. The face that is directly exposed to various external factors such as ultraviolet (UV) radiation and pollution makes it highly susceptible to hyperpigmentation.[1] Acquiring bright and white skin is a desirable outcome for patients particularly in Asia.[2] To combat various hyperpigmentation disorders, it is imperative that we inhibit the melanogenesis pathway.[3]

Currently, the gold-standard treatment for hyperpigmentation is hydroquinone (HQ). However, long-term HQ use is associated with a variety of adverse disorders, including

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ochronosis and cancer.[3,4] Therefore, decades of research have been dedicated to an alternative depigmenting agent with better safety profile and equal or greater efficacy than HQ. In order to achieve this goal, several agents such as cysteamine, tranexamic acid, Galctomyces ferment filtrate (GFF) and niacinamide have been studied.[5]

Cysteamine, which is derived from the amino acid L-cysteine, is known to inhibit the melanogenesis process.[6] While tranexamic acid has long been used as inhibitor of plasmin activation antagonist that can decrease epidermal pigmentation and correct dermal structural changes in melasma patients.[7] GFF is a species of yeast that is frequently used in cosmetics. It acts as an anti-oxidant that help reduces skin pigmentation and oxidative stress.[8] Niacinamide is a water-soluble vitamin B3 amide that possesses an inhibitory effect on melanosome transfer.[9–12]

This study aims to assess the effectiveness of topical serum and cream containing 1% cysteamine, 3% tranexamic acid, 2% Galactomyces ferment filtrate, and 4% niacinamide using double layering technique to brighten facial skin through examination of chromameter and Janus-III facial skin analyzer.

Methods

This study is an open label pre-posttest clinical trial conducted between May 2021–January 2022.

Subjects were women aged 31-50 years with type IV Fitzpatrick skin who visited the Dermatology outpatient clinic at Hasanuddin University Hospital and Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, Indonesia. Exclusion criteria included pregnancy or breastfeeding, menopause, undergoing hormonal therapy or on systemic tranexamic acid in the past three months, and suffering from chronic inflammatory disease of the facial skin. All subjects signed informed consent forms and research was carried out according to the Helsinki Protocol and obtained ethical clearance from Hasanuddin University, Makassar, South Sulawesi, Indonesia.

At the initial visit (W0), the L* values and pigmented spots of the face were measured using chromameter and the Janus-III Facial Analysis System, respectively. Participants were then instructed to wash their faces in the evening and apply two drops of serum containing 1% cysteamine, 3% tranexamic acid, 2% GFF, and 4% niacinamide for one minute, followed with application of one fingertip unit (FTU) of cream containing the same ingredients. Participants were then instructed to wash their faces and apply SPF 35 sunscreen in the morning. Subjects were evaluated for eight weeks over the course of four sessions with a two-week interval (W1, W2, W3, W4). At each visit, an evaluation of L* and pigmented spot was performed.

Chromameter® Chromameter® (Konica Minolta, Japan) is an instrument for objectively measuring skin colour by analysing the reflection of a xenon lamp perpendicular to the probe at 450, 560, and 600nm. The obtained parameters are represented by L*, a*, and b* values. The L* value parameter is used to depict the skin colour's brightness (100 for white and 0 for black).[13]

Janus-III Facial Analysis System® Janus-III Facial Analysis System® (PIE Inc, South Korea) is a facial analysis device that employs a high-resolution camera to objectively analyze different skin conditions, such as pigmented spots, skin wrinkles, skin tone, UV spots, and sebum levels.[2]

Software Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc.) was utilised for data analysis. For the L* and pigmented spot parameters, descriptive analysis was performed by calculating the mean and standard deviation at each visit, followed by the Wilcoxon test to assess the effects of treatment within eight weeks. Results are presented in the form of tables and graphs.

Results

A total of 70 subjects took part in the trial with an average age of 37.8 years. **Table 1** and **Figure 1** illustrate changes in L* values over a period of 8 weeks. We found that there was a consistent increase in the average of L* value at each visit with a baseline score of 52.10 at W0 and a mean average of L* value of 56.40 at W4. (p=0.00).

Furthermore, through Janus-III Facial Analyzer, we found that the average number of pigmented spots on the face significantly decreased from 45.52 to 43.90 at the end of the trial **(Table 2** and **Figure 2)**. This decrease was significantly noted starting at W4 of treatment (p=0.01).

Adverse reactions and tolerability A total of eight patients (11.4%) in this study reported local pruritus on areas applied and twelve patients (17.1%) complained of a pungent odour. No erythema or irritation were reported during the course of the trial.

Discussion

The color of human skin is influenced by various pigments, predominantly by melanin produced by the melanocytes in the melanogenesis pathway. This process is influenced by both internal factors such as aging, and external factors, most notably UV radiation. The presence of unwanted hyperpigmentation is a major cosmetical problem.[13,14]

There are various methods to measure hyperpigmentation. The parameters produced should be able to be measured objectively to be able to assess treatment efficacy. The chromameter is a practical, well-standardized non-invasive measuring tool that has long been

Table 1 Comparison of L* value within 8 weeks of treatment.

Session (W)	*L* Value Mean ± SD*	*P-Value*
0	52.10 ± 4.03	-
1	53.74 ± 3.77	0.00
2	55.19 ± 3.58	0.00
3	55.61 ± 3.54	0.00
4	56.40 ± 3.51	0.00

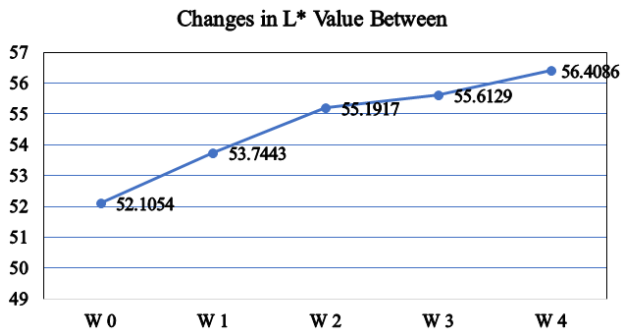

Figure 1 Consistent Increase in L* Value

Table 2 Comparison of pigmented spot within 8 weeks of treatment.

Session (W)	*Pigmented Spot Mean ± SD*	*P-Value*
0	45.52 ± 16.30	-
1	47.43 ± 15.80	0.99
2	45.84 ± 15.50	0.23
3	46.24 ± 14.80	0.00

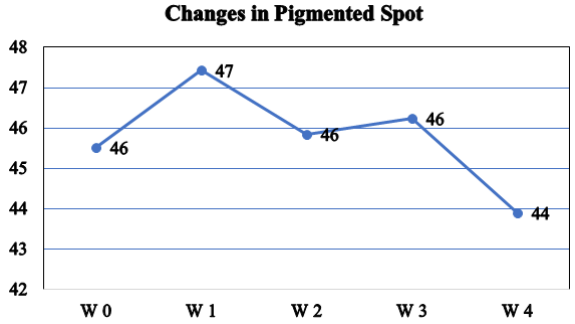

Figure 2 Improvement in pigmented spot noted on W4.

used to evaluate, among others, the level of melanin (L* value) and hemoglobin (A* value).[13]

Recently, new devices such as the Janus-III facial analyzer system have the ability to evaluate overall facial skin characteristics such as pigmented spots, sebum, wrinkle, pores, etc. Previous studies have found that the Janus-III device is most useful in measuring pigmented spot of both the upper and lower dermis through evaluation of polarized light sources and UV light. Scores obtained can then be classified into five grades (I-V). In addition, it is also the most commonly used imaging analysis device used in Korea.[2,15]

Cysteamine hydrochloride is a well-known non-mutagenic and non-melanoctotoxic depigmenting agent that has long been explored as a safer option to HQ for melasma. It is hypothesized that cysteamine works by interfering the action of the tyrosinase enzyme essential in the melanogenesis pathway.[6] In our study we found that the use of a lower concertation of cysteamine (1%) compared to the more commonly studied concentration (5%) proved to be both efficacious and well-tolerated by subjects by producing a consistent improvement in L* value and pigmented spots with milder reported adverse effects.[6,16]

However, it should also be noted that higher concentration of cysteamine in previous studies were used for treatment of melasma compared to as brightening agent for aging skin such as in this trial. The current study found consistent increase in L* value indicating brighter skin in every measuring session, with an overall 5.40-point increase over 8 weeks of treatment. The depigmenting efficacy is further supported by a mean decrease of 1.62 points in facial pigmented spots notably starting at week-8 of constant treatment.

The rationale regarding the use of double-layering technique by applying serum followed with cream may act as an initial barrier preventing rapid absorption of active ingredients, therefore preventing, or reducing possible side-effects that may hinder the patient's tolerability and adherence.[17] The study regarding double-layering technique in dermatology is still limited. A recent study regarding the use of double-layering as wound dressing found that bilayer wound dressing can mimic the epidermal and dermal layers of the skin and is effective in the skin repair process.[18]

A study by Karrabi, *et al.* evaluated the use of 5% cysteamine cream compared to modified Kligman's formula found a lower modified melasma severity index (mMASI) score in subjects receiving cysteamine after 12 weeks for treatment of epidermal melasma (7.04 and 6.09 respectively).[16] However, conflicted results regarding the efficacy of cysteamine compared to HQ were also reported as demonstrated by another study by Lima, *et al.* that found that the improvement of mMASI score by 5% cysteamine was inferior to 4% HQ (24% and 41% respectively).[19] In both studies however, the reported side-effects produced by cysteamine use were consistent. This include erythema, xerosis, scaling, irritation and burning sensation.[16,19] The current study found that there were reduced adverse effects limited to foul odor (17.1%) and pruritus (11.4%) with no noticeable erythema or irritation reported.

In addition, the combination of cysteamine with other active ingredients such as tranexamic acid, niacinamide, and GFF further compliment the depigmenting efficacy. Tranexamic acid is a trans-4-(aminomethyl) cyclohexane carboxylic acid that has long been used as a fibrinolytic agent that inhibits the plasmin/plasminogen pathway in the melanogenesis process and hinders melanocyte-keratinocyte interaction after UV radiation.[20,21] Recent studies on topical

tranexamic acid have found that it is especially effective as a depigmenting agent for UV-induced hyperpigmentation, including melasma. A study in Iran conducted in 2014 found that 3% tranexamic acid compared to HQ+ dexamethasone evaluated using split-face method found no significant differences in efficacy, with more notable side-effects found on HQ use for 12 weeks.[22] In terms of use as a brightening agent, a recent study in 2020 reported that the use of newer tranexamic acid derivatives such as cetyl tranexamate mesylate produced a 16.9% improvement in melanin index on both males and females after 8 weeks of use in sun-damaged skin when applied twice daily.[23]

Niacinamide, a well-known depigmenting agent works by inhibiting melanosome transfer as well as acting as an antioxidant that helps reduce melanin production. The substance also possesses antiaging properties.[24,25]

GFF acts as an antioxidant that also increases the level of natural moisturizing factors through expression of the aryl hydrocarbon receptor that upregulates filaggrin, therefore aiding in suppressing the inflammatory response towards cysteamine.[26]

Conclusion

The double layering technique using serum and cream containing lower concentration of cysteamine combined with tranexamic acid, niacinamide, and GFF is a promising depigmenting combination regiment that produces great depigmenting effect while reducing commonly reported side effects of cysteamine such as irritation and erythema.

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