THE EFFECTIVENESS OF COMBINATION SERUM OF TRANEXAMIC ACID, GALACTOMYCES FERMENT FILTRATE, NIACINAMIDE AND ALPHA ARBUTIN IN ENHANCING SKIN BRIGHTNESS

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ABSTRACT Introduction: Light skin tone has been desired by many Asian women thus the search for effective depigmenting agent. Tranexamic acid, an antifibrinolytic drug, is now gaining popularity as a new depigmenting agent. However, studies on tranexamic acid have shown the mixed result of its comparison to hydroquinone. Galactomyces ferment filtrate, niacinamide and alpha arbutin have been known of their depigmenting effect. Combined materials with different targeting mechanisms are used to enhance the effectiveness of the lighting agent. **Objective:** To compare the skin lightening effect of the combination of tranexamic acid 3%, galactomyces ferment filtrate 2%, niacinamide 4%, and alpha arbutin 2% to hydroquinone 4%. **Methods:** In this study, each of 30 participants applied a combination of tranexamic acid 3%, galactomyces ferment filtrate 2%, niacinamide 4%, and alpha arbutin 2% and hydroquinone 4% to the left forearm using a particular patron. The subject then evaluated each week for four weeks. Clinical effects were evaluated using a chromameter including L* for skin brightness and a* for skin erythema. All measurements were taken three times, and the mean value was used. To assess the comparison of skin brightness score and pigmentation intensity between the two serum groups, the Independent T-test was used. As for assessing the change in scores based on measurement time in each serum group, Pearson's Correlation was used. The test results are significant if the value of $p < 0.05$. **Results:** Skin brightness (L*), as measured by chromameter, when sample first came (T0) on the area applied with serum combination of tranexamic acid 3% got the average of brightness of skin 56,81, whereas in the area applied 4% hydroquinone got the average brightness of skin 55,66. In the last control of the area applied a serum combination of 3% tranexamic acid had an average skin brightness of 58.34 and the area applied with 4% hydroquinone serum had an average skin brightness of 57.48. There was a significant increase of skin brightness of the skin both in the area applied with tranexamic acid 3% ($p < 0.05$) serum combination and in the area applied with hydroquinone 4% serum ($p < 0.01$). The degree of decreased a* score was higher in combination with tranexamic acid 3% serum than hydroquinone serum, i.e. 0.314 compared to 0.221. **Conclusion:** Serum combination of tranexamic acid 3%, galactomyces ferment filtrate 2%, niacinamide 4% and alpha arbutin 2% can be considered as a safe and effective option to increase skin brightness with no significant side effect.

KEYWORDS depigmenting, tranexamic acid, galactomyces ferment filtrate, niacinamide, alpha arbutin

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Introduction

Human skin colour is one of the most apparent phenotypic variations among humans and is determined primarily by the type and amount of melanin synthesized in melanosomes and the distribution patterns of melanosomes in melanocytes. Getting brighter skin tone has attracted much interest in the world, especially for the dark-skinned groups in Asia and Africa with the Fitzpatrick IV-V skin type. [1] Recognizing the increasing need for brighter skin, many products have been developed to brighten the skin. Hydroquinone is the gold standard for skin lightening agents but the safety concerns on the use of hydroquinone/ are associated with some side effects such as exogenous ochronosis, pigmentation of the eyes and nails, and in some cases corneal damage. [2,3] This encourages researchers to find other agents for hyperpigmentation.

The introduction of tranexamic acid as skin lightening is a relatively new concept. Tranexamic acid inhibits melanin synthesis in melanocytes by interfering with the interactions of melanocytes and keratinocytes through inhibition of the plasminogen / plasmin system, which decreases the activity of tyrosinase and leads to decreased melanin synthesis by melanocytes. [4] The results of some studies showed that the application of single topical tranexamic acid 3% has successfully decreased the MASI score in melasma patients. [5,6] The previous study of tranexamic acid produced conflicting data when it was compared to hydroquinone. In this study, we used tranexamic acid with a combination of several other depigmentation agents to produce better skin lightening products.

Combined materials with different targeting mechanisms are used to enhance the effectiveness of the lighting agent. Skin pigmentation regulation occurs at various levels, and different interferences are required. The combination approach is thought to be more successful than simply targeting tyrosinase. [7] Galactomyces ferment filtrate is known to reduce the appearance of skin pigmentation by reducing melanin synthesis and oxidative stress in melanocyte cells. [8] Niacinamide has been known to inhibit the transfer of melanosomes from melanocyte cells to keratinocytes. [9,10] Arbutin has a mechanism of action of melanosomal tyrosinase inhibition at non-toxic concentrations. [11] We want to use these agents in combination with a tranexamic acid to produce an effective lightening agent. Thus, this study aims to evaluate the skin lightening effect of the combination of tranexamic acid 3%, galactomyces ferment filtrate 2%, niacinamide 4%, and alpha arbutin 2% compared to hydroquinone 4%.

Methods

This double-blind, randomized controlled clinical trial was done at dermatovenereology clinic at Hasanuddin University Hospital, Makassar, between April to May 2018. The subjects were explained the study, and those who agreed were asked to sign an informed consent form (Ref. Number; 215/ H4.8.4.5.31/ PP36-KOMETIK/ 2018 from Hasanuddin University Ethics Committee). In total 30 subjects, aged from 25 to 50 years, with skin phototypes III to V according to Fitzpatrick's classification, were included in the study. Exclusion criteria were pregnancy/lactation, the presence of other dermatoses on the arm, history of hypersensitivity to a substance used in this study, use of any aesthetic medical procedures or depigmenting agents on the face within one month before the study, and use of systemic tranexamic acid within three months before the study.

All patients enrolled in the study were instructed not to apply any other product on their arms beside the agents used in this study. Subjects in the experimental group received a topical serum formulation containing a combination of tranexamic acid (containing tranexamic acid 3%, galactomyces ferment filtrate 4%, niacinamide 2% and alpha arbutin 4%) and hydroquinone 4% as a control. Serum combination of tranexamic acid and hydroquinone were placed in two identical containers coded as A and B. To ensure the serum was applied to the same site; a special patron was made. The patron was made of elastic material with two holes, with the distance of the first hole (A) located 4 cm from cubital fossa, and the second hole (B) located 4 cm from the first hole. The patron was then placed on the outer side of the left forearm. Serum A was then applied on the first hole (A), and serum B applied to the second hole (B). In the morning and evening, each subject applied one drop of each serum to the applying site. The subject then evaluated each week for four weeks.

Standardized photographs were taken at a fixed position and a fixed distance from the applying site. Skin pigmentation and erythema were measured using a chromameter (CR-400, Minolta, Japan). The chromameter provides 3 variables L*, a*, and b*, brightness ranging from 0 (black) to 100 (white), a* (degree of redness), and b* (variation in color between blue and where lower values indicate a darker skin and higher values a lighter skin). All measurements were taken three times, and the mean value was used. Standardized photographs, chromameter measurement and adverse effects (AEs) were assessed at baseline and during each visit.

Data analysis was performed using SPSS version 22. To assess the difference in skin brightness and pigmentation intensity between the two serum groups, an Independent T-test was used. Change in scores based on measurement time in each serum group was measured using Pearson's Correlation was used. The test results are significant if the value of $p < 0.05$.

Results

All 30 subjects completed the study in four weeks. No subjects discontinued their participation due to lack of effectiveness or adverse events. The mean L* value, as measured by chromameter at baseline (T0) and each follow-up per week (T7, T14, T21, T28), were shown in Table 1.

At baseline, the mean value of L* on the area applied with combination serum of 3% tranexamic acid at baseline was 56,81, whereas in the area applied with 4% hydroquinone was 55,66. In the final follow-up, the mean value of L* on the area applied with combination serum of 3% tranexamic acid was 58,34 and the area applied with hydroquinone 4% serum was 57,48. Based on these data, there was a significant increase of mean L* value at both sites applied with serum combination of tranexamic acid 3% ($p < 0.05$) and at the area applied with 4% hydroquinone ($p < 0.01$) from baseline to final follow-up timepoint at week 4 (Table 2). There was not any significant difference in the means of L* value between the tranexamic acid and hydroquinone area at all visits and at the end of follow-up.

In table 3, there was a significant decrease in a* score in both groups ($p < 0.05$). The degree of decreased a* score was higher in

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Table 1 Changes in Skin Brightness (L*) value on both areas in all visits.

Time of measurement	Area	n	Mean	SD	P=value
T0	Tranexamic acid 3% combination	30	56,81	2,66	0,085
	Hydroquinone 4%	30	55,66	2,42	
T7	Tranexamic acid 3% combination	30	57,42	2,79	0,132
	Hydroquinone 4%	30	56,36	2,58	
T14	Tranexamic acid 3% combination	30	57,83	2,80	0,098
	Hydroquinone 4%	30	56,68	2,50	
T21	Tranexamic acid 3% combination	30	58,10	2,79	0,092
	Hydroquinone 4%	30	56,93	2,45	
T28	Tranexamic acid 3% combination	30	58,34	2,77	0,219
	Hydroquinone 4%	30	57,48	2,56	

Table 2 The total increase in Skin Brightness (L*) value.

Area	R	P-value
Tranexamic acid 3% combination	0,190	0,020
Hydroquinone 4%	0,236	0,004

Table 3 Changes in a* value throughout the study.

Area	R	P-value
Tranexamic acid 3% combination	-0,314	0,000
Hydroquinone 4%	-0,221	0,007

a combination of 3% tranexamic acid serum than hydroquinone serum, i.e. 0.314 compared to 0.221. There was no significant change of b* score parameter in both groups ($p > 0.05$).

There were no side effects in both products, and the subjects in this study well tolerated them.

Discussion

There is a high demand for safe and effective skin depigmentation agents. The previously accepted gold standard skin depigmentation agent, hydroquinone, has some frequently reported adverse events. Because of this potential health risk, in 2001 hydroquinone was banned from the use of cosmetic products thereby encouraging the effort to find new depigmentation agents. Among them, it is generally recognised that arbutin, ascorbic acid, azelaic acid, kojic acid, licorice, niacinamide, and galactomises ferment filtrate have skin depigmentation properties. However, much research has been done still at the in vitro level for most of these agents, and there is still no controlled clinical trial data. [12,13]

In Table 1 there was an increase in skin brightness from week 1 (T7) to week 4 (T28) in both groups receiving serum combination of 3% tranexamic acid and 4% hydroquinone serum. In this study, the group receiving a combination of 3% tranexamic acid showed a higher skin brightness score on T7, T14, T21 and T28 compared to the 4% hydroquinone group, although this difference is not statistically significant ($p > 0.05$). This data suggested that tranexamic acid combination serum is as effective as hydroquinone in promoting skin depigmentation. This finding is consistent with previous studies showing the effectiveness of topical tranexamic acid as a depigmentation agent in melasma therapy where MASI score was reduced with no side effects observed.[5,12,14,15] An in-vitro study of human melanocyte cells given galactomyces ferment filtrate 5% every two days showed 35% melanin decrease in 25 days. [8] Studies on niacinamide have demonstrated melanosomal transfer suppression resulting in decreased skin pigmentation and 4% niacinamide is an effective agent for the treatment of melasma. [16] In a study conducted by Lee et al. there was a reduction of facial hyperpigmentation after combination therapy of tranexamic acid and niacinamide. [17] A study showed that applying 2% alpha-arbutin for one month was effective in brightening the skin. [18]

Table 2 showed that there was a significant increase in skin brightness in both areas applied with tranexamic acid 3% serum ($p < 0.05$) and in the area applied with hydroquinone 4% serum ($p < 0.01$). The results of this study are by the research conducted by Banihashemi et al. over 12 weeks compared the MASI score reduction more in the group applied with 5% tranexamic acid cream compared to the group applied with hydroquinone 4%

cream, although not statistically significant. [13] Research by Afeti et al. which compared topical tranexamic acid 5% with hydroquinone 2% in melasma treatment also resulted in a similar 12-week MASI score reduction by both groups. [19]

In table 3, there was a significant decrease in a* score in both groups ($p < 0.05$). The degree of the decreased score was higher in tranexamic acid than Hydroquinone, i.e. 0.314 compared to 0.221. Previous reports have also shown that tranexamic acid reduces erythema in melasma skin, as it is associated with a decrease in the number of blood vessels in the dermis. The anti-angiogenic or anti-inflammatory effects of tranexamic acid have been reported. [20] Research by Kim et al. indicating a topical tranexamic acid application was found a consistent a* decrease in the chromameter examination. [15]

Conclusion

Serum combination of tranexamic acid 3%, galactomyces ferment filtrate 2%, niacinamide 4% and alpha arbutin 2% can be considered as a safe and effective option to increase skin brightness with no significant side effect.

Competing Interests

There were no financial supports or relationships between authors and any organisation or professional bodies that could pose any conflict of interest.

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