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A Split-Face Comparative Study in Efficacy and Safety between the Combination of 4% Niacinamide and 4% Kojic Acid Cream versus 4% Hydroquinone Cream for Epidermal Melasma

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ABSTRACT

Background: Melasma is a hyperpigmentation disorder that affects the quality of life, especially in women. Hydroquinone has remained the mainstay of melasma treatment. However, its safety for long-term usage became a great concern. Combination therapy, such as niacinamide and kojic acid, can be used as an alternative melasma treatment due to different mechanisms of action and synergism. **Purpose:** The aim of this study was to compare the efficacy and safety of a combination of 4% niacinamide and 4% kojic acid (N-K) vs. 4% hydroquinone (HQ) in epidermal melasma. **Methods:** This was a randomized, double blind, clinical study on 13 female epidermal melasma patients at the Cosmetic Dermatology Outpatient Clinic of Dr. Hasan Sadikin Hospital, Bandung. Patients received two creams, a combination of N-K and HQ, for split-face therapy, regardless of the sides of the face. All patients were followed up at 4 and 8 weeks. The clinical efficacy was assessed for skin lightening effects using a spectrophotometer (L* value) and the melasma area severity index (MASI). Adverse effects were assessed in all patients. **Result**: Both the N-K and HQ groups showed significant improvement in skin lightening and MASI scores on week 8 ($p < 0.05$). There was no statistically significant difference in efficacy between the N-K and HQ groups ($p > 0.05$). None of the patients in the N-K group complained of any adverse effects. Whereas in the HQ group, 23.07% presented with pruritus and mild erythema. **Conclusion:** The combination of 4% niacinamide and 4% kojic acid was similar to 4% HQ in efficacy and had a promising safety profile.

Keywords: hydroquinone, kojic acid, melasma, niacinamide.

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BACKGROUND

Melasma, sometimes referred to as chloasma, is an acquired pigmentary condition that occurs commonly on sun-exposed areas, especially the face.[1,2,3] It is characterized as light-brown to dark-brown hyperpigmented macules,[1] usually symmetric in distribution with irregular borders.[2] It has a significant impact on patients' quality of life, causing frustration and depression due to its frequent facial involvement.[4] Melasma is very common in females,[1,2,5] approximately around 90%,[2] mainly seen in reproductive years and rarely before puberty.[2,5] The exact prevalence of melasma is unknown, but it affects predominantly Southeast Asians (40%).[1,2]

The pathogenesis of melasma is complex and not completely understood.[1] Genetics, hormonal activity, and ultraviolet (UV) exposure play key role in melanin deposition in melasma.[1,5] Recently, vascular factors such as the interaction of proangiogenic factors and melanocytes might play an important role in the development of melasma.[6,7] Melanin synthesis occurs in melanocytes in several steps, consists of

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melanogenic protein transcription, melanin synthesis inside melanosomes catalyzed by tyrosinase, and the last critical step, melanosomes transfer from melanocytes to surrounding keratinocytes.[8] In melasma, hyperactivity of melanocytes, influenced by genetics, hormones, UV exposure, and vascular factors, results in increased amounts of melanin.[2]

Based on the location of the melanin pigment deposition, melasma is divided into epidermal, dermal, and mixed types.[1,2] Epidermal melasma is more responsive to topical therapy.[1,3] The principles of melasma therapy include photoprotection from UV light,[2,9] melanin synthesis suppression, inhibition of melanosome transfer to keratinocytes and removal of melanin deposits.[9] Most depigmenting agents are tyrosinase inhibitors, including hydroquinone, kojic acid, azelaic acid, alpha-hydroxy acid, arbutin, mequinol, liquorice extract, and ascorbic acid.[2,3] Other skin depigmenting agents inhibit melanosome transfer, including soy bean extracts and niacinamide.[10]

Hydroquinone, mainly used in concentrations of 2–5%, remains the first line therapy for epidermal melasma and acts as a tyrosinase inhibitor.[2] However, its safety and side effects remain a concern due to its unstable form, ochronosis, irritant contact dermatitis, and post-inflammatory hyperpigmentation.[3] Thus, this has encouraged research into alternative topical agents for the management of melasma. Combination therapy consists of several compounds with different mechanisms of action and synergistic effects that are considered more effective compared to single agents.[11]

Kojic acid is a fungal metabolic product (*Aspergillus*, *Penicillium*, and *Acetobacter*) that acts as a tyrosinase inhibitor.[2,12] Its preparation is commonly used at concentrations of 2-4% and often combined with other depigmenting agents.[12] Niacinamide, or nicotinamide, a niacin (vitamin B3) derivative that inhibits melanosome transfer from melanocytes to keratinocytes and is commonly used in concentrations of 4-5%.[13]

This study aimed to evaluate the comparison in efficacy and safety between a combination of 4% niacinamide and 4% kojic acid cream versus 4% hydroquinone cream for epidermal melasma. In this study, the melasma area severity index (MASI) score and spectrophotometer were used to assess treatment response.

METHODS

This was a randomized, double-blind, split-face clinical study on 13 epidermal melasma of female patients at the Cosmetic Dermatology Outpatient Clinic, at the Dermatology and Venereology Department of Dr. Hasan Sadikin Hospital, a teaching and tertiary referral hospital in Bandung, West Java, Indonesia. Written informed consents were taken from all patients. Personal and medical histories were obtained, and a clinical examination were done. Photographic images (frontal, right, and left views) with a digital camera were taken. Epidermal melasma was classified by clinical and Wood's lamp examination. Methods of assessment pre- and post-treatment involved evaluation of skin lightening using the luminosity axis (L*), as measured by a spectrophotometer (Konica Minolta CM-700d), and the MASI score.

Female patients with bilateral facial epidermal melasma were included in this study. The exclusion criteria of this study were patients who had a history of hypersensitivity to hydroquinone, niacinamide, or kojic acid; pregnant women and lactating mothers; took hormonal contraceptives; used topical treatment (depigmenting agent, tretinoin, and corticosteroid) within the last two weeks; took systemic corticosteroid within the last one month; had laser treatment, microdermabrasion, and chemical peeling within the last three months; and had skin inflammation in the facial area.

The faces of the patients were divided into halves (right and left sides), and each half was randomly assigned to receive 1 fingertip unit (FTU) or approximately 0.5 grams of a combination therapy cream containing 4% niacinamide and 4% kojic acid (referred to as the N-K group). The other halves were treated with 1 FTU or approximately 0.5 grams of 4% hydroquinone cream (referred to as the HQ group). The creams were applied once daily at night for a duration of eight weeks.In addition, all patients were instructed to apply a sun protection factor (SPF) 30 sunscreen daily before engaging in any outdoor activities, to avoid direct sun exposure, and to use a physical sun protector such as a hat or umbrella to cover their facial area.

Patients were evaluated at the fourth and eighth weeks. Improvement was assessed with clinical photographs, a spectrophotometer, and the MASI score at each visit, and any adverse effects were noted. The L* value indicates skin lightness, with values from 0 (black) to 100 (white) evaluated using a spectrophotometer. MASI was developed by Kimbrough-Green et al.[14] for the assessment of melasma. The severity of the melasma in the four regions (forehead, right malar region, left malar region, and chin) is assessed based on: the percentage of the total area involved (A), darkness (D), and homogeneity (H). The numerical value assigned to A is as follows: 0 = no involvement; 1 = <10% involvement; 2 = 10 − 29% involvement; 3 = 30 − 49% involvement; 4 = 50

− 69% involvement; 5 = 70 − 89% involvement; and 6 = 90 − 100% involvement. D is graded from: 0 = (normal skin color without evidence of hyperpigmentation) to 4 = (severe). H is graded as follows: 0 = (normal skin color without evidence of hyperpigmentation) to 4 = (uniform skin involvement without any clear areas). Total MASI score counted as: forehead 0.3 (D+H) A + right malar 0.3 (D+H) A + left malar 0.3 (D+H) A + 0.1 chin (D+H) A. Any adverse events, including pruritus, burning, erythema, edema, erythematous papules, bullae, urticaria, post-inflammatory hyperpigmentation (PIH), and ochronosis, were observed throughout the study.

All data were analyzed by the Shapiro-Wilks test to determine the normality of the data distribution. Categorical variables were analyzed using the Chi-square. Numeric variables were assessed using the paired-T test. P-values less than 0.05 were considered significant. All analyses were performed using SPSS software. This study has been approved by the Ethics Committee at Dr. Hasan Sadikin Hospital No. LB.02.01/C02/579/III/2016.

RESULT

A total of 13 females who had bilateral epidermal melasma with a mean age of 48.84 years were included in this study (Table 1). The patterns of melasma seen were malar in 7 patients (53.85%) and centrofacial in 6 patients (46.15%). The mean onset of melasma was 44.23 years. The average duration of melasma was 4.84±3.02 years. Most of the patients (92.3%) had 2 hours of sun exposure daily. Ten patients (76.9%) never use sunscreen or sun protection. All patients had a family history of melasma. Other risk factors, such as a history of using hormonal contraceptives, were present in 3 patients (23.07%), and a lesion appeared during pregnancy in 1 patient (7.69%).

The skin lightening effect (L* value), as measured by a spectrophotometer, was performed initially at 4 weeks and at the end of the study (8 weeks). The average baseline of L* value in the N-K group and the HQ group were 49.13±14.776 and 53.53±4.002, respectively. At 4 weeks, there was a significant increment in the L* value in the N-K group, which was 53.85±3.976 ($p<0.05$). Further, there was no significant change in the HQ group, which was 53.97±4.205 ($p>0.05$). After 8 weeks, L* value exhibited significant improvement in both the N-K and HQ group, which were 55.94±3.531 ($p=0.0001$) and 56.32±3.854 ($p=0.001$), respectively (Table 2).

The average baseline MASI score in the N-K group and the HQ group was 4.476±2.029 and 4.615±1.777, respectively. The MASI score in both groups showed improvement at 4 weeks: but was not statistically significant ($p>0.05$), it was 4.269±2.046 in the N-K group and 4.430±1.602 in the HQ group. At the end of 8 weeks, The MASI score was reduced to 3.600 with N-K and 3.876 with HQ. P values for the MASI score at 8 weeks for both N-K and HQ were 0.0001 and 0.001, respectively (Table 2).

Table 1. Patient demographic data and disease characteristics

Study Parameters	n=13	%
Gender		
Males	0	0
Females	13	100
Age (in years)		
36-45	5	38.46
46-55	4	30.77
56-65	4	30.77
>65	0	0
Clinical pattern		
Centrofacial	6	46.15
Malar	7	53.85
Mandibular	0	0
Duration of daily sun exposure (hours)		
0-2	12	92.30
3-4	1	7.7
>4	0	0
Family history of melasma		
Yes	13	100
No	0	0
History of hormonal contraceptive use		
Yes	3	23.07
No	10	76.93

Table 2. Comparison of skin lightening effects using the spectrophotometer (L* value) and MASI score between both groups (baseline, week 4, and week 8)

Variable	Spectrophotometer (L* value)		MASI score	
	N-K group	HQ group	N-K group	HQ group
Baseline				
Mean±SD	49.13±14.776	53.53±4.002	4.476±2.029	4.615±1.777
Week 4				
Mean±SD	53.85±3.976	53.97±4.205	4.269±2.046	4.430±1.602
P value*	0.006	0.600	0.095	0.165
Week 8				
Mean±SD	55.94±3.531	56.32±3.854	3.600±1.779	3.876±1.672
P value*	0.0001	0.001	0.0001	0.001

*Freidman test; SD, standard deviation

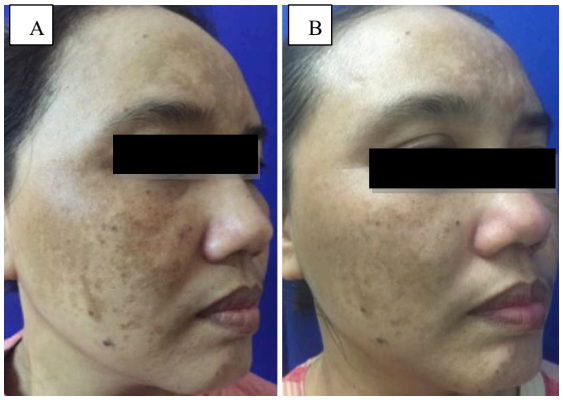

Figure 1. Patient no.1, (A) 0 weeks before treatment initiation; (B) After using a combination therapy of 4% niacinamide and 4% kojic acid cream at 8 weeks.

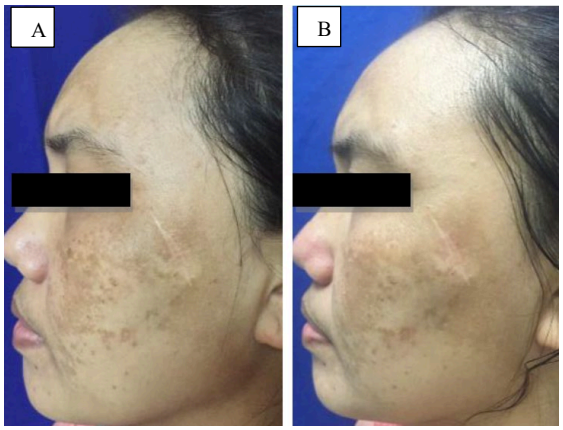

Figure 2. Patient no.1. (A) 0 weeks before treatment initiation; (B) After using 4% hydroquinone cream at 8 weeks.

Patients in both groups showed significant improvement in melasma with N-K and HQ. A statistical comparison of the efficacy between both groups revealed that there was no difference based on L* value increment ($p>0.05$) and MASI score reduction ($p>0.05$). Delta of L* value increment pre- and post- treatment in the N-K group and the HQ group were 3.08 and 2.94, respectively. Whereas the delta of MASI score reduction in the N-K and HQ groups was 0.88 and 0.65, respectively. It implies that N-K was similar to HQ in efficacy (Table 3). Clinical improvement is seen in the photographs (Figures 1, 2).

No serious adverse effects were noticed. Out of 13 patients, only 3 patients (23.07%) complained of side effects, all in the HQ group. Pruritus was present in 1 patient (7.6%) and mild erythema in 2 patients (15.3%). None of the patients detected any stinging sensation, edema, ochronosis, or darkening on the drug-applied areas. We observed no clinically meaningful adverse effects during the treatment and follow-up periods (Table 4).

Table 3. Efficacy comparison of N-K and HQ based on skin lightening effects (L* value) increment and MASI score reduction

Variable	Group		
	N-K Group n=13	HQ Group n=13	P value*
L* value increment	3.08±1.371	2.94±2.422	0.701
MASI score reduction	0.88±0.798	0.65±0.763	0.399

*Wilcoxon test

Table 4. Adverse effect

Variable	Group		
	N-K Group n=13	HQ Group n=13	P value*
Pruritus	0	1	
Stinging	0	0	
Mild erythema	0	2	
Edema	0	0	
Ochronosis	0	0	
Hyperpigmentation	0	0	
Total	0	3	0.066

*Fisher exact test

DISCUSSION

Our study included 13 females aged 37-58 years with melasma, and the obtained sample showed similar epidemiological characteristics to a previous study by Solis et al.[15] conducted in 27 females aged 25-53 years. In a study conducted by Sardesai et al.[3], the prevalence of melasma is higher in females over 40 years compared to males. The high prevalence of melasma in females might be attributable to hormonal influences such as pregnancy, hormonal contraceptives, and cosmetic use.[3] Melasma commonly occurs in middle-aged adults over the third decade of life.[4] The mean age of onset in our study was 44.23 years. Yalamanchii et al.[4] reported that the mean age of onset was 37.13 years. Therefore, the obtained sample well reflects the epidemiological pattern of the occurrence of melasma.

According to the distribution of lesions, two clinical patterns of melasma were observed, and among these, the malar type was the most common, seen in 7 patients. The other type noted was centrofacial, seen in 6 patients. This was similar to the study by Monteiro et al.[12] where the most common clinical pattern of melasma was malar type (73%). Among the study population, there was no patient with the mandibular type. Similar to the study by Sardesai et al.[3], none of the patients had mandibular type.

Multiple causative factors have been implicated in the etiology of melasma, including sun exposure, genetic predisposition, and hormonal activity.[5,16] Most of the cases (12 out of 13 patients) had 2 hours of sun exposure daily. This is consistent with the study conducted by Halder et al.,[17] which found that the majority of their patients (68%) had 2-4 hours of sun exposure daily. UV exposure stimulates melanogenesis.[11] α-melanocyte stimulating hormone (MSH) binds to the melanocortin 1 receptor (MC1R) on the surface of melanocytes and thereby modulates melanin synthesis through the activation of the cAMP-dependent protein kinase A pathway.[18] Thus, photoprotection is essential in melasma treatment. Based on the literature, 65% of patients reported not using sunscreen when melasma symptoms appeared.[19] Similarly, in our study, we also found that 10 patients never use sunscreen or any other form of photoprotection.

A positive family history of melasma was observed in all patients and which was in correlation with earlier reported studies, varied from 33.33% to 70%.[3,5,15] Melanogenesis is regulated by different genes, including epidermal growth factor receptor (EGFR), OMPR1, and single nucleotide polymorphisms (SNPs), which are associated with melasma risk. In this study, 23.07% of patients took hormonal contraceptives. Similar findings were observed in another study by Solis et al.[15], which reported hormonal contraceptives usage among 29% of patients. It appears that hormonal contraceptives are a significant contributing factor in melasma.[5] Several hormones, including MSH, estrogen, and progesterone, stimulate melanogenesis by increasing tyrosinase transcription and dopachrome tautomerase.[20]

Combination therapy is the preferred mode of melasma treatment for its synergism and reduction of untoward effects.[11] The topical triple combination known as Kligman's formula has gained popularity among the general population for various purposes.[21,22] The original formula included a mild steroid, dexamethasone 0.1%, in combination with 0.1% tretinoin and 5% hydroquinone in a cream base. This formula has been modified over the years to suit

different skin types.[22] The use of this triple combination in patients with melasma has increased significantly in recent years, and as a result, the side-effect profile has also come to light. A study conducted in Saudi Arabia involving a total of 292 participants with a mean age of 26.9 years reported that skin redness was the most commonly mentioned side effect of Kligman's formula (61.6%), followed by a burning sensation (50.7%).[21] A study in 20 melasma patients in India using modified Kligman's regimen for 8 weeks showed the most common adverse effects were acneiform eruption, erythema, and burning.[22] Uncontrolled and long-term use of hydroquinone can cause exogenous ochronosis. The majority of these reports included patients who had used high concentrations of hydroquinone on large areas of skin numerous times a day for years at a time.[23] Thus, other combination formulas should be considered when treating melasma.

Deo et al.[24] conducted a study comparing different topical agents with a combination of kojic acid, hydroquinone, and corticosteroid for melasma treatment in 12 weeks. The best clinical response, in terms of reduction of the MASI score, was observed in a combination agent of 1% kojic acid and 2% hydroquinone.[25] Hydroquinone and kojic acid are tyrosinase inhibitors that inhibit hydrolyzation of tyrosine to dihydroxyphenylalanine (DOPA), oxidization of DOPA to DOPAquinone, and decarboxylation of DOPAchrome to 5,6-dihydroxyindole **(**DHI) or DHI-carboxylic acid (DHICA).[2,8] During skin pigmentation, melanosomes are transferred from melanocytes to keratinocytes.[8] Niacinamide acts by preventing the transfer of melanosomes to keratinocytes.[3,11] Thus, the combination of these two agents gives better therapeutic melanogenesis results compared to monotherapy as a result of their different actions on different stages of melanogenesis.[11]

Our results showed that a 4% niacinamide and 4% kojic acid cream combination was effective to treat melasma and showed similar efficacy compared to 4% hydroquinone cream. The skin lightening effect of 4% niacinamide and 4% kojic acid cream on baseline was 49.13. It is significantly evident as early as 4 weeks of treatment, and at 8 weeks, it was 53.85 and 55.94 ($p<0.05$), respectively. Similar to the study conducted by Solis et al.[15] wherein 4% niacinamide showed 44% increment in lightening effect at 8 weeks. Whereas in the HQ group, skin lightening effects showed significant results in 8 weeks ($p<0.05$) compared to 4 weeks ($p>0.05$).

The reduction of the MASI score was higher in the N-K group as early as 4 weeks ($p=0.095$) compared to the HQ group ($p=0.165$). At 8 weeks, both groups showed similar statistically significant results ($p<0.05$). Shariati et al.[25] reported similar efficacy between 2% hydroquinone and 4% kojic acid based on MASI score evaluation. The topical combination used in this study produced similar satisfactory results compared to monotherapy, presumably due to a different mechanism of action.

Concerning the adverse effects, hydroquinone had mild adverse effects found in 23.07% of patients. The most frequent side effects were pruritus and mild erythema. Combination therapy of niacinamide and kojic acid showed no side effects and was well tolerated. Similar results from a prior study, which revealed that erythema and pruritus were higher on the hydroquinone side compared to the kojic acid side, at 3.3% and 6.7%, respectively, were also reported.[12] Niacinamide is considered a very safe nutrient and is well tolerated by the skin at the normally used concentration. Unless used long-term at very high doses orally, it may cause side effects in the liver or other organs.[25] Whereas in kojic acid, adverse reactions may appear with long-term use of KA, such as sunburn in sensitive skin.[27]

Combination therapy of 4% niacinamide and 4% kojic acid appears to be an effective and safe treatment for melasma. It could be a promising therapeutic agent as an alternative to hydroquinone. Our limitations were the subjective assessment of the MASI score and the amount of cream applied by participants. However, further studies with a larger sample size are required to identify the ideal formulation and evaluate the efficacy of combination agents in the treatment of melasma.

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