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Effectiveness of Combination TranexamicAcid 3% and Nicotinamide 3% with Microneedling in the Treatment of Melasma

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Abstract:
Introduction*:Melasma is a facial hyperpigmentation that is common in women and areas frequently exposed sunlight that chronic and recurrent. Kligman formula therapy is still the effectivetreatment but has several side effects especially for long-term use. The combination of tranexamic acid therapy, nicotinamide and microneedling is an alternative therapy for melasma that safe and effective for the long term.*
Objective:*This study aimed to evaluate the efficacy of the combination 3% tranexamic acid, 3% nicotinamide, and microneedling versus Kligman's formula in reducing melanin index*.
Materials and Methods*:This experimental pre and post control group design was conducted in 28 melasma patients, group A received a topical cream combination of 3% tranexamic acid and 3% nicotinamide with microneedling compared with group B received a modified Kligman's formula (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide). The efficacy of the treatments was determined through the Mexameter® at baseline, week fourth, eighth and twelfth. The statistical analysis used the chi-square test. The p-value of <0,05 statistically significant.*
Results*:The melanin index showed a decrease in both groups without statistically significant difference between them (p> 0.05). The decrease in melanin index difference in group A has shown its effectiveness significantly in week 8 to week 12, whereas in group B started to be significant at week 12..*
Conclusion*:The combination therapy of tranexamic acid cream 3%, nicotinamide 3%, and microneedling was as effective as the modified Kligman formula (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%) in decreasing the melanin indeks*
Keywords : *microneedling, melasma, nicotinamide, tranexamic Acid*

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I. Introduction

Melasma is a hypermelanosis of the skin characterized by the appearance of irregular brown macules, varying in size, symmetrically distributed in areas that are often exposed to sunlight.[1]Melasma is a hyperpigmentation disorder that is often encountered that acquired, chronic and recurrence.[2]

Melasma usually occurs in women although men can also be affected, but the incidence is rarely less than 10%.[3]Melasma occurs in women of reproductive age (20-45 y.o) although this condition can occur in men and often occurs in tropical countries.[1,4]The causes of melasma are multifactorial such as genetics, sunlight, age, sex, hormones, pregnancy, thyroid dysfunction, cosmetics and drugs that cause an increase in melanogenesis in melanocytes.[5,6]One of the important factors influencing melasma is ultraviolet (UV). The diagnosis of melasma based on clinical features and supporting examination.[1,3]

Therapy of melasma patients is protect causative factors, use of sunscreen, use of depigmentation agents and laser therapy but have different effectiveness and side effects.[7]Study by Chan et al. (2008) reportedthat there was an improvement in melasma patients with Kligman's formula based on the investigator's assessment of the Global Severity Score and Melasma Area Severity Index (MASI) score but this study also reported side effects.[8]

Some therapeutic modalities such as topical depigmentation agents, chemical peels, dermabrasion and laser therapy have been used in different studies with unsatisfactory results. Therapeutic options for melasma to be developed, one of which is the use of tranexamic acid.[1,9]Another therapeutic agent for melasma is nicotinamide, which has an effect on reducing pigmentation through reducing melanosome transfer, photoprotection, anti-inflammatory and anti-aging effects by reducing the presence of solar elastosis.[10]There has not been scientific evidence yet about the combination of topical nicotinamide and. Microneedling for melasma

therapy. Microneedling is one of the adjuvant therapies in melasma. Budamakuntla et al. (2019) reported that combination of tranexamic acidand microneedling was safe and effective for melasma.[9]In paracrine, TGF-β is a strong inhibitor of the secretion of hepatocyte growth factor (HGF) from fibroblasts that plays a role in melasma.[11]This study aimed to evaluate the efficacy of 3%tranexamic acid,3% nicotinamide and microneedling is more effective than the Kligman formula in reducing the melanin index in melasma patients.

II. Material and Methods

This clinical experimental pre and post control group study was performed in 28 subjects. These subjects were divided into 2 groups, 14 patients in group A received the combination of 3% tranexamic acid and 3% nicotinamide topical cream with microneedling and 14 patients in group B received modified Kligman's formula (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide). The efficacy of the treatments was determined through the Mexameter® at baseline, week fourth, eighth and twelfth. An unpaired statistical t-test was used to compare the efficacy of both two groups if the data distribution is normal and homogenous. Mann-Whitney test was used if the data distribution is abnormal. All analyses were performed using SPSS version 20computer software for Windows and p value < 0.05 was considered statistically significant.

III. Result

Table 1. Sociodemographic Characteristics

Characteristics	Group		Total	p Value
	Group A	Group B		
Age				0.015
20-30 y.o	1 (7.1%)	2 (14.3%)	3 (10.7%)	
31-40 y.o	4 (28.6%)	10 (71.4%)	14 (50.0%)	
41-50 y.o	9 (64.3%)	2 (14.3%)	11 (39.3%)	
Education				0.063
Elementary school	5 (35.7%)	2 (14.3%)	7 (25.0%)	
Middle School	5 (35.7%)	3 (21.4%)	8 (28.6%)	
High school	4 (28.6%)	9 (64.3%)	13 (46.4%)	
Occupation				0.222
Security	0 (0.0%)	3 (21.4%)	3 (10.7%)	
Cleaning Service	14 (100.0%)	11 (78.6%)	25 (89.3%)	
Family History of Similar Sickness				0.45
Yes	6 (42.9%)	8 (57.1%)	14 (50.0%)	
Not	8 (57.1%)	6 (42.9%)	14 (50.0%)	
History of Hormonal Contraception				0.445
Yes	5 (35.7%)	7 (50.0%)	12 (42.9%)	
Not	9 (64.3%)	7 (50.0%)	16 (57.1%)	
Previous Drug Use History				0.385
Yes	5 (35.7%)	2 (14.3%)	7 (25.0%)	
Not	9 (64.3%)	12 (8.,7%)	21 (75.0%)	
Clinical pattern				0.669
Malar	6 (42.9%)	5 (35.7%)	11 (39.3%)	
Centrofacial	8 (57.1%)	9 (64.3%)	17 (60.7%)	
Melasma type				1.000
Epidemal	6 (42.9%)	6 (42.9%)	12 (42.9%)	
Mix	8 (57.1%)	8 (57.1%)	16 (57.1%)	

Based on Table 1, the most age groups in this study were 31-40 y.o (50%). In group A, the most were aged 41-50 y.o, 9 patients (64.3%), while group B had the most age 31-40 y.o, 10 patients (71.4%). The Mann Whitney test result obtained p value = 0.015 (p <0.05) there are significant differences in the characteristics of the research subjects based on age between group A and group B. The most education in this study was a high school of 13 patients (46.4%). The majority of subjects had education background finished their study from high school (46.4%). The occupation was mostly cleaning service (89.3%). In the study, there were 14 people (50%)

who had a family history of similar diseases. Most of the subjects (25%) had received treatment from aesthetics clinics or buy over the counter products. The centrofacial clinical pattern is more common in group B (64.3%), the same as in group A (57.1%). Mixed melasma type was the highest in group A patients (57.1%) as well as group B (57.1%).

Table2. Value of melanin index improvement in both groups

Treatment	Mean of Melanin Index			
	Week 0	Week 4	Week 8	Week 12
Group A	334.76 ±48.84	329.80 ±49.81	323.73 ±41.63	318.23 ±40.49
GroupB	326.87 ±53.73	316.94 ±50.79	317.72 ±43.87	302.59 ±46.79
p-*value*	0.215	0.232	0.713	0.353

Group A = Combination of 3% tranexamic acid and 3% nicotinamide with microneedling
Group B = Modified Kligman formula (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%)
p Value = Have a significant difference when p <0.05

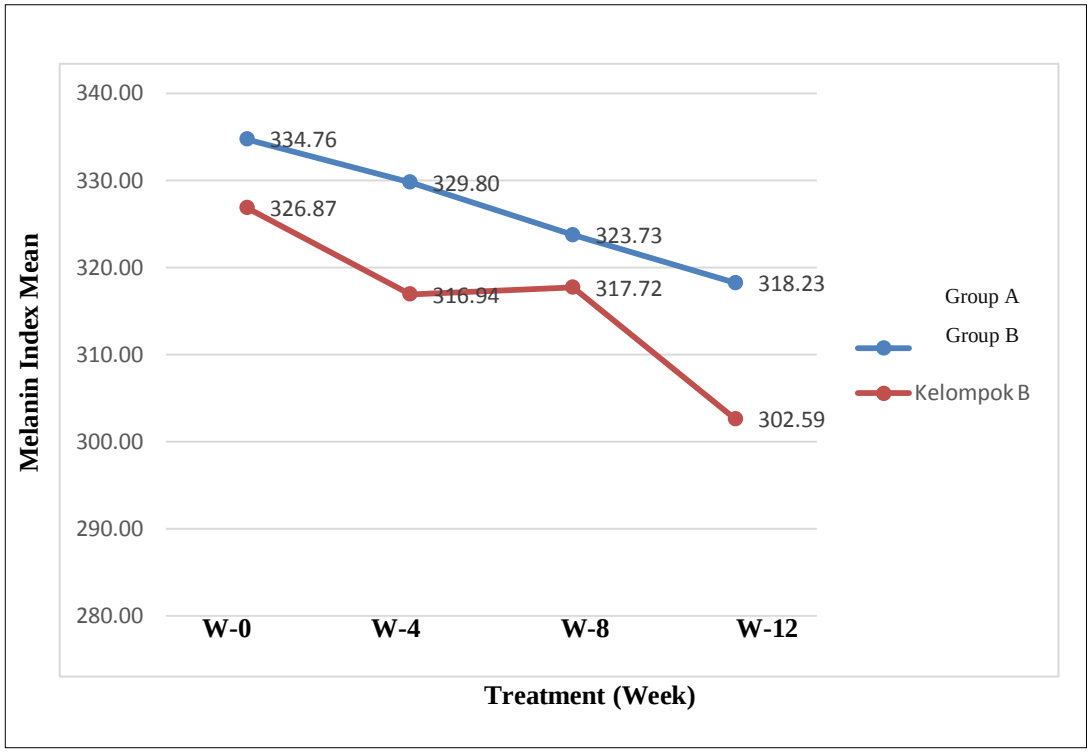

Figure 1. Changes in mean melanin index in both groups

Figure 1 shows the mean of melanin index in both groups has decreased. According to Table 3, the difference between the two groups was not statistically significant.

Table3.Difference in Change in Melanin Index

Group	Difference in Melanin Index					
	W4-W0		W8-W0		W12-W0	
	Difference	p	Difference	p	Difference	p
Group A	-4.95 ±21.50	0.397	-11.02 ±21.06	0.048	-16.53 ±24.35	0.026
Group B	-9.93 ±19.58	0.096	-9.15 ±27.30	0.245	-24.29 ±26.38	0.003
p	0.527		0.841		0.426 [a]	

Group A= Combination of 3% tranexamic acid and 3% nicotinamide with microneedling
Group B = Modified Kligman's formula (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%)
pValue = a significant difference $p < 0.05$

Based on Table 3, there was a significant difference in melanin index at week 8 ($p = 0.048$) and week 12 ($p = 0.026$) in group A, while group B had a a significant differencein melanin index at week 12 ($p = 0.003$).

IV. Discussion

This study compared a topical cream containing a combination of 3% tranexamic acid and 3% nicotinamide with microneedling to a modified Kligman formula (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%) in melasma patients. Tranexamic acid is a novel therapy in the management of melasma by inhibiting melanogenesis through inhibition of the plasminogen / plasmin pathway. Tranexamic acid in 85 Korean women significantly reduced the mean MASI score from 13.22 to 7.57 at week 12.[1,12]A study by Kim found that the use of tranexamic acid in melasma with 23 subjects for over 12 weeks had significant results in terms of decreasing melanin index andMASI score.[13]Another study by Steiner, evaluating the efficacy of using topical and injected tranexamic acid states that the use of topical 3% tranexamic acid cream applied twice daily for 12 weeks is resulted in significantly decrease in melasma lesions.[14]

In melasma, nicotinamide plays a role in skin pigmentation by decreasing the regulation of melanosome transfer from melanocytes to keratinocytes.[15]Nicotinamide may also reduce regulation of the number of melanosomes transferred from melanocytes to keratinocytes by 35% to 68%.[16]Nicotinamide can induce a reduction in pigmentation, inflammation (mast cell infiltration) and solar elastosis and is a safe therapy with minimal side effects compared to hydroquinone.[10]Nicotinamide has side effects such as burning sensation and skin irritation after the use of this compound that usually occur in the first 3 days of use, pruritus, erythema and burning sensation.[10]A randomized double blind study conducted by Lee et al evaluated the efficacy of a combination of 2% nicotinamide and 2% tranexamic acid as a topical moisturising formulation in the treatment of facial hyperpigmentation in 42 Korean women stated that there was a significant decrease in melanin index and also had a skin lightening agent effect.[17]Another study conducted by Navarette et al in a randomized double blind study comparing the effectiveness of nicotinamide 4% and hydroquinone 4% in the treatment of melasma showed that both of these therapies showed show significant improvements.[10]

Microneedling is one of the adjuvant therapies in melasma.[18,19]Microneedling in melasma therapy can be an intradermal delivery of topical drugs, where the stratum corneum is the main barrier for drug penetration.[9,20]The study by Budamakuntla et al. comparing microneedling tranexamic acid and microinjection tranexamic acid showed a more significant improvement in tranexamic acid with microneedling.[9]microneedling works in repairing melasma patients through the mechanism of a number of micro-wounds that directly stimulate the release of various growth factors, namely platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor-α (TGF-α) and transforming growth factor-β (TGF-β). Paracrine, TGF-β is a strong inhibitor of the secretion of hepatocyte growth factor (HGF) from fibroblasts that plays a role in melasma.[21]The mechanism of action of microneedling as a melasma therapy is by activating melanocytes, keratinocytes and epidermal growth factors to optimize the function of epidermal and melanogenesis, normalizing the success of microneedling as melasma therapy by activating melanocytes, keratinocytes and epidermal growth factors so as to optimize the function of epidermal and melanogenesis. Between keratinocytes and melanocytes that regulate melanosome transfer, normalize the differentiation of melanocytes through the activation of mitogen protein kinases so that the dendritic arm is more flexible.[22]

A study by Chan et al. (2008) showed an improvement in the severity of melasma based on the investigator's assessment of the Global Severity Score and a decrease in the MASI (Melasma Area Severity Index) score using the Kligman formula, but this study also reported minor side effects such as erythema, irritation, exfoliation and skin discomfort.[8]Hydroquinone is used at concentrations of 2-5%, but the most beneficial is a concentration of 4%.[23]Hydroquinone inhibit tyrosinase activity and has a toxic effect on melanocytes. Hydroquinone derivatives include mecquinol and arbutin.[1]Although hydroquinone has been considered a gold standard for treating melasma, this drug is claimed satisfying but unsafe because the side effects such as erythema, stinging, millium colloids, allergic and irritant contact dermatitis, nail discoloration, hypermelanosis and exogenous ocular inflammation.[24,25]The Kligman formula also contains retinoid. As we knowretinoid inhibit the tyrosinase enzyme, reducing hyperpigmentation by stimulating melanin release through increased epidermal turnover, reducing melanosome transfer from melanocytes to keratinocytes by reducing contact time and reduce melanogenesis through inhibition of tyrosinase transcription.[1,26]The common side effect of retinoid is irritation or redness and sometimes hyperpigmentation on peeling areas[15]The mechanism of corticosteroid is to inhibit the synthesis of mediators like prostaglandins and leukotrienes that have an effect on melanogenesis, it can also inhibit melanin synthesis by decreasing general cell

activity.[1]Corticosteroid can reduce irritation or inflammation caused by hiroquinone and tretinoin. The side effects of high potency corticosteroid, especially in the long term if given as monotherapy can cause epidermal atrophy, telangiectation, acne or acne eruption, rosacea-like erythema, perioral dermatitis and itching.[27]

Evaluation of therapy in this study using mexameter® MX 18 to measure the melanin and erythema index. Both groups saw a decrease in melanin index at the end of the visit compared to the beginning of the visit. Melanin index reduction in the two groups showed no significant difference. This explains that administration of tranexamic acid cream 3% and nicotinamide 3% with microneedling showed the same effectiveness as depigmentation with the modified Kligman's formula (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%) on the melanin index results.

The decrease in melanin index difference in group A has shown its effectiveness significantly in the 8th week to the 12th week, whereas in group B it only started to be significant at 12th week. The melanin index of group A was significantly greater than group B du to mechanism of action of tranexamic action. The tranexamic acid in cream A inhibits the melanogenesis process by modulating hydroxylation of tyrosine to DOPA, while plasmin inhibitor[8] and nicotinamed play role in down regulation of melanosome transfer from melanocytes to keratinocytes.[15] Decreasing of melanin index was observed significantly faster at week 8 to week 0. Vice versa hydroquinone in cream B acts as depigmentating agent by inhibiting tyrosinase enzyme, where DOPA has already produced in the skin. Thus condition effects slow reduction of melanin index and observed at week 12 to week 6. The combination of topical 3% tranexamic acid and 3% nicotinamed cream with microneedling (group A) was greater in melanin index reducing compare to modified Kligman formula in Group B.

V. Conclusion

The combination therapy of topical 3% tranexamic acid and 3% nicotinamide with microneedling was as effective as the modified Kligman formula in melanin index reducing.The melanin index decreasing was significantly different at week 8 and 12.

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