The safety and efficacy of 5% Niacinamide cream for infraorbital hyperpigmentation

Chaw Su Su Han[1], Tanomkit Pawcsuntorn[2]

[1,2]Anti-aging and Regenerative Medicine

Corresponding author: Email 6452001001@lamduan.mfu.ac.th

(Received: October 3, 2024; Revised: October 20, 2024; Accepted: November 9, 2024)

Abstract

Infraorbital hyperpigmentation becomes a significant concern in individual regardless of gender and age. The etiology of infraorbital hyperpigmentation is multifactorial including excessive pigmentation, periorbital volume loss, skin laxity and density of subcutaneous vasculature. Moreover, its management is quite challenging because multiple factors contribute this condition and choosing the appropriate treatment according to the causative factors. Among the causes, excessive pigmentation due to increased melanin is the most common factor. Niacinamide, one of the active forms of vitamin B3, possesses various properties such as skin lightening effect, anti-inflammatory, antioxidants and sebostatic effect. However, no clinical study that demonstrating the safety and efficacy of 5% Niacinamide cream for infraorbital area.

Keywords: Infraorbital Hyperpigmentation; 5% Niacinamide Cream; Mexameter

1. Introduction

Infraorbital hyperpigmentation has been defined as periorbital hyperpigmentation and dark circles. It significantly become the common patients' concern especially in woman in both dermatology and aesthetic field. It affects in all ages regardless of gender and race. Although it is not affecting directly our organ damage, it can impact on our quality of life since it make individual appearance looked old, tired and even sad (*Safety.Pdf*, n.d.).

There are multifactorial factors to cause infraorbital hyperpigmentation. Excessive pigmentation is the main cause triggered by dermal melanocytosis and post inframammary hyperpigmentation after atopy or allergic dermatoses. The causes of dermal melanocytosis are congenital lesions like Nevus of Ota, prolonged sun exposure and certain drugs. Thin, translucent eyelid skin is another cause of infraorbital hyperpigmentation and appear as violaceous color. In addition, overhanging of the lower eyelid muscle and fat makes more prominent the appearance of dark circle (Roh & Chung, 2009).

There are many treatment options available for infraorbital hyperpigmentation in nowadays. Topical, chemical peeling, injection, laser, and surgery procedures are available for management for dark circles. Chemical peeling method is used for depigmentation of dark circles which control skin damage, rejuvenation, and generation of tissues. There are many peeling agents with superficial, medium and deep

depth depending on the concentration. Trichloroacetic acid, alpha-hydroxy acid such as glycolic acid are common peeling agents (Roh & Chung, 2009).

Various lasers are utilized such as Q-switched ruby laser (694nm), Q-switched Alexandrite (755nm), Q-switched Nd:YAG (1064), pulsed-dye laser and ablative or non-ablative laser. There are selective photo-thermolysis action, collagen rejuvenation effect in different laser systems. To retore the volume loss, autologous fat transplantation and hyaluronic filler injection are the main choice of treatment (Friedmann & Goldman, 2015).

Topical depigmenting agents are the easy, cheap and effective options which are hydroquinone, kojic acid, arbutin, niacinamide and vitamin C. The mechanism of depigmentation is inhibition of tyrosinase enzyme, preventing melanocyte hyperactivation and decreasing the melanin transfer. Combination with topical agents with different actions gives more effective results (Sawant & Khan, 2020).

Although there are plenty of evidence-bases research for melasma and facial whitening, a relatively small number of scientific studies to support infraorbital hyperpigmentation. Moreover, most of the studies were related to the tyrosinase inhibitory of skin lightening compounds, but fewer research related to different action on melanogenesis like niacinamide.

Niacinamide are water soluble vitamin and amide form of vitamin B3. It plays the critical role in NADH and NADPH which are the main enzyme of the body metabolism. Moreover, it possesses many other abilities such as anti-inflammation, anti-wrinkle, reduced sebum production and barrier protection (Wohlrab & Kreft, 2014). There is no side effect to the organ and no drug resistant have been reported. Because of fewer side effect, cheap and easy to apply, niacinamide become high demand ingredient in cosmetics.

Research approved that niacinamide compound is beneficial in facial skin whitening. Therefore, this study will be conducted in order to see its efficacy of 5% niacinamide cream for infraorbital hyperpigmentation with any possible adverse effects.

2. Research Objective

(1) To observe the efficacy of 5% Niacinamide cream for the treatment of infraorbital hyperpigmentation.

(2) To observe the adverse effect of 5% Niacinamide cream in infraorbital hyperpigmentation to observe the participants' satisfactory score of 5% Niacinamide cream

3. Literature Review

3.1 Theory, Concept and Related Research

3.1.1 General information

Niacinamide can be observed in free as well as in bound form in plants and animal tissue, primarily as part of the pyridine nucleotides nicotinamide-adenine dinucleotide (NAD) and nicotinamide-adenine dinucleotide phosphate (NADP). It is taken with food. Approximately 500 ppm can be found in yeast, between 10 and 100 ppm in various bacteria, alfalfa, oat, maize, wheat, palm kernel oil, soya beans, molasses, and in animal organs like liver, kidneys and muscles. After the co-enzymes have separated,

niacinamide is resorbed almost completely in the small intestine. After resorption niacinamide is stored as NAD in the liver, therefore the homoeostasis of the niacinamide in serum is regulated. Niacinamide is excreted through the kidneys. (Wohlrab & Kreft, 2014)

3.1.2 Mechanism of Action

The physiologic role of niacinamide is as a precursor to important co-factors: (NAD) and its phosphate derivative (NADP) which involve as redox co-enzymes in many enzymatic reactions and antioxidants and have other signaling properties. Therefore, it is possible that niacinamide has these multiple effects on skin indirectly because of its role as a co-enzyme precursor. The effect of topical niacinamide is inhibition of oxidative processes such as protein oxidation (glycation). Glycation is a spontaneous oxidative reaction between protein and sugar resulting in cross-linked proteins that are yellowish-brown in color and are fluorescent. These products can accumulate in matrix components such as collagen that have long biological half-lives.(Bissett et al., 2004) As the precursor of nicotinamide adenine dinucleotide (NAD), which a major coenzyme in the production of adenosine triphosphate (ATP). ATP is known as cellular energy currency that transports chemical energy within cells and boosts cellular energy and may enhance energy-dependent cellular processes such as DNA repair. In addition, Niacinamide is the sole substrate and an inhibitor of the nuclear enzyme poly- ADP-ribose polymerase 1 (PARP-1), which is activated by UV radiation. PARP-1 proposes several important cellular properties, such as DNA repair and genomic stability, as well as the regulation of some transcription factors, particularly with relation to the expression of inflammatory cytokines, chemokines, adhesion molecules and inflammatory mediators. When PARP-1 is overexpressed or NAD may be over-consumed, leading to cellular dysfunction or necrosis. Having adequate cellular energy and properly functioning PARP-1 is crucial for a number of skin conditions, for which niacinamide may have beneficial effects.(Chen & Damian, 2014)

3.1.3 Uses and Adverse effect

Apart from depigmentation, both oral or topical niacinamide has multiple properties such as antioxidant, antiwrinkle, anti-acne and dermatological skin diseases. For this reason, it grows to be the popular ingredient in skin care products. There are many studies related to niacinamide for different clinical purposes.

The clinical 3-year retrospective study of bullous pemphigoid treatment with tetracycline, nicotinamide, and lesionally administered clobetasol (TNC) in comparison to prednisone (P). The median period between complete remission and relapse was 60 days in the TNC group and 90 days in the P group. At least one relapse within 1 year was noted in 32.1% of patients from the TNC group and 50% from the P group. The 1-year survival for the TNC and P groups was 83% and 65.9%, respectively, and the 3-year survival was 71.2% and 48% respectively. In conclusions Tetracycline and nicotinamide combined with lesionally administered clobetasol is an alternative, effective treatment with better survival rates compared to prednisone in BP.(Chaidemenos, 2001)

In a double-blind randomized control trial, in patients with four or more actinic keratosis, the development of basal cell carcinomas and actinic keratosis reduced significantly when patients took oral nicotinamide (500 mg twice daily for 4 months) compared to those who were given a placebo. (Surjana et al., 2012)

Side effects from the topical application of nicotinamide are minor and rare and include mild burning, pruritis, and erythema. These side effects improve with continued use. Meanwhile, adverse effects of oral form include liver toxicity, neurotoxicity when using high doses. (Rolfe, 2014).

However, their association have not been studied well for infraorbital hyperpigmentation. That is why, we would like to observe more about adverse effect after topical application of Niacinamide.

3.1.4 Related Research

There are some studies of niacinamide related to hyperpigmentation.

The study by (Hakozaki et al., 2002) is randomized split-face double-blind paired design using vehicle moisturizer on both sides of the face to 18 Japanese women aged 25-60 years. They observed the outcomes of applying 5% Niacinamide cream vs the vehicle moisturizer twice daily for 8 weeks duration. By using image analysis and visual assessment, the side of the face receiving niacinamide showed a significant reduction in hyperpigmentation compared to the side receiving the vehicle.

Another study with 50 participants of age 40-60 years by (Bissett et al., 2004)tested 5% Niacinamide moisturizer versus placebo control for 12 weeks duration. Double-blind, placebo-controlled, split-face study with left-right randomization was conducted in healthy Caucasian female subjects to reveal the improvement of aging skin including wrinkle, hyperpigmented spots and blotchiness. They found that there is improvement in the appearance of facial skin texture, wrinkle, and hyperpigmentation as well.

This research by (Kimball et al., 2010) is a 10-week, double-blind, vehicle-controlled, full-face, parallel- group clinical study conducted in 101women aged 40–60 years. They compared a daily regimen of either a morning sun protection factor (SPF) 15 sunscreen moisturizing lotion and evening moisturizing cream each containing 4% niacinamide + 2% NAG vs the SPF 15 lotion and cream vehicles by measuring with chromophore-specific image analysis based on noncontact SIAscopyÔ, they found that the niacinamide + NAG formulation regimen was significantly more effective than the vehicle control formulation.

(Lee et al., 2014) conduct clinical study of total of 42 Korean women used a twice-daily regimen of either a moisturizing cream containing 2% niacinamide + 2% TXA or cream vehicles. Pigmentation was measured objectively using a mexameter and chromameter and found that combination regime was significantly more effective than the vehicle.

Another research by (Bissett et al., 2009) conducted two groups for 10 weeks treatment randomized, split-face clinical studies. In one study, a vehicle control and a 5% niacinamide formulation (n= 40), or a 5% niacinamide and a 5% niacinamide plus 1% N- undecylenoyl phenylalanine formulation was applied and in second study, one of the three emulsion: vehicle control, 5% niacinamide formulation, or combination 5% niacinamide plus 1% N-undecylenoyl-phenylalanine formulation was used. After using

quantitative image analysis, they found that the combination of 5% niacinamide and 1% N-undecylenoyl phenylalanine is an effective.

Research approved that niacinamide compound is beneficial in skin whitening. Therefore, it is inevitable that niacinamide is effective for hyperpigmentation for face but there is no study related to infraorbital hyperpigmentation with statistic evident data and the safety for eye area. In addition, many studies showed that there are almost no side effects of 5% Niacinamide to use in face so in this study we will conduct for the safety and efficacy for 5% Niacinamide cream. We will focus on the efficacy with the use of standardized measurements of melanin index.

3.2 Research Framework

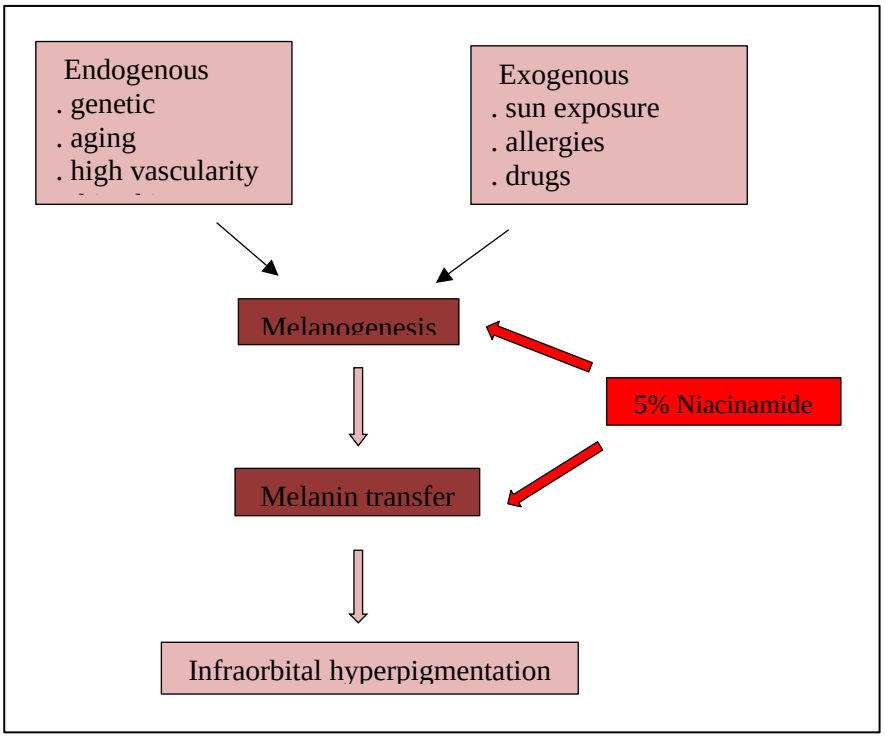

Figure 1 Research Framework

3.3 Research Hypotheses

5% Niacinamide cream can effectively reduce infraorbital hyperpigmentation.

4. Research Methodology

4.1 Research Design

This study is an open-labeled assessor blinded clinical trial.

4.2 Population and Sample

Patients aged 20-50 years, both male and female was evaluated by dermatologists that dark circles caused by pigmentation. Fitzpatrick's skin type 2-5 participants willingly to get treatment and can come to monitor the treatment.

The study of efficacy of 5% Niacinamide cream on treatment of infraorbital area has never been established & published before, so the researcher find as a similar article, which is a study of effectiveness of a combination of anti-pigmentary products including niacinamide for facial post-inflammatory hyperpigmentation by (Nayak et al., 2019) sample to show the statistically significant result on the purpose of the study.

The mean melanin index shows a significant drop from 473.4 $\pm$ 123.7 before intervention to 358.2 $\pm$ 112.2 after 90 days of intervention of facial post-inflammatory hyperpigmentation measured by Mexameter.

$\mu d = 473.4 - 358.2 = 115.2$

$S_1 = 123.7.$ $S_2 = 112.2$

$n_1 = 114,$ $n_2 = 114$

From the formula, $\alpha = 0.05$ (two-tailed), $Z_{0.025} = 1.96$, $Z_{0.1} = 1.28$

$S_p^2 = [(n_1-1) S_1^2 + (n_2 -1) S_2^2] / n_1 + n_2 - 2$

$S_p^2 = [(114-1) (123.7)^2 + (114-1)(112.2)^2] / (114+114 - 2)$

S_p^2 (pooled variance) = 13945.265

To calculate the sample size by two mean dependences, using formula

$$n = (Z\alpha_{/2} + Z\beta)^2 \sigma^2 / (\mu_1 - \mu_2)^2$$

Set

n = 0.05 (two tailed) Z = 1.96

n = 0.10 (one tailed) Z = 1.28

$n = (1.96 + 1.28)^2 (13945.265) / (115.2)^2$

$= 11.030 \approx 11$

Where

n = sample size

$S = \sigma$ = Variance

$S^2_p = \sigma^2$ =Pooled variance

The expected dropout rate is 30%. Thus, 15 volunteers (n=15) should be recruited.

4.3 Selection Criteria

4.3.1 Inclusion criteria

- healthy male and female volunteers aged between 20-50 years old.
- volunteers are well-being and have no problems around the eye.
- Fitzpatrick skin phototype 2-5
- Volunteers who acknowledge not to apply any periorbital whitening cream during 12 weeks of study.

- volunteers who agree not to do facial filler injection, any laser treatment and surgery around the periorbital area during the study.
- volunteer who accepts to follow the guidelines, daily use of the cream and give consent by signing the written consent.
- participants who are willing to obtain this research and regular follow up for 3 months.

4.3.2 Exclusion criteria:

- Subjects with birth marks the eyelid area.
- Subjects with marked eye bags or marked wrinkle (we put these one because it is not true hyperpigmentation but due to shadowing effect)
- subjects with ocular diseases
- subjects who are in pregnant or plan to have conception.
- breastfeeding mother
- subjects who have allergic reaction history to niacinamide cream
- subjects who have allergic or hypersensitivity reaction history to any cosmetic components
- subjects who got eye filler procedure, peeling and any ablative or non-ablative laser treatment 6 months before the study
- subjects' career or work environment is performed under the sun for some period of time
- volunteers who develop more than + score in patch test
- subjects who have open wounds, any skin lesions around the infraorbital region
- subjects who have epilepsy
- subjects are taking any medication which oppose the melanogenesis such as OC pill, phenytoin and spironolactone.

4.3 Research Instrument

1. 5% niacinamide
2. Patch test
3. VISIA®Complexion Analysis System (Canfield, Fairfield, NJ)
4. Mexameter ®MX 18 (Courage-Khazaka Electronic, Koln, Germany)
5. Consent paper
6. Patient record form
7. Adverse effect record form
8. Letter of qualification
9. Satisfactory evaluation questionnaire for both doctors and volunteers

4.4 Data Collection

To record the data of mean melanin index, VISIA®Complexion Analysis System, the Global Satisfaction Score, participants' satisfaction score and adverse effects, and examination will be performed. This will be carried out at Mae Fah Luang University Hospital, Bangkok.

General data such as age, sex, address, occupation, previous medical and surgical history, and previous and current treatments for infraorbital hyperpigmentation will be recorded.

Record melanin index assessed by Mexameter ®MX18 in the lower eyelid area before treatment and during the study at 4th,8th and 12th weeks by dermatologists.

Assess the efficacy of 5% niacinamide for infraorbital hyperpigmentation using VISIA®Complexion Analysis System before and after the study.

Evaluate the satisfaction and assessment scoring system by three dermatologists (the researcher, Dr. May Su Than and supervisor) using the Global Satisfaction Score ranging from -1 to +4 in which

-1 means worse,
0 means no improvement,
+1 means fairly improvement (1-25%),
+2 means moderate improvement (26-50%),
+3 means good improvement (51-75%) and
+4 means excellent improvement (76-100%).

Evaluate the patient's satisfaction by using grading system after the study at 12 weeks. The scores range from -1 to +4 in which.

-1 means worse,
0 means not improved,
+1 means fairly improve (1-25%),
+2 means moderate improve (26-50%),
+3 means good improve (51-75%) and
+4 means (76-100%).

Record patient's adverse effects by answering questionnaires and dermatologist' observation at every visit. To evaluate the adverse effects, researcher asked every participant about pruritus score from 0 to 10, duration of erythema, other side effects like contact dermatitis and post inflammatory hyperpigmentation and hypopigmentation. If any adverse effect related to the research occurred while applying the cream, participants can contact the researcher in any time and giving them the contact information of the researcher like phone number and email.

4.5 Data Analysis

Volunteers are recruited in order to the inclusion and exclusion criteria and their personal information was highly confidential.

The data analysis of volunteers' medical records and outcomes are conducted by using Microsoft Excel 2010 in Mae Fah Luang University Dermatology Clinic.

The general demographic data of participants were recorded using descriptive analysis with supplying descriptive information like percentages, means, median, modes, ranges and standard deviations.

5. Research Findings

Total 15 volunteers participated in this study in which the mean age was 28.4 ± 2.1 ranging from 25-32years and 12 students as well as 3 employers enrolled. There were 2 Fitzpatrick skin type III, 11 in skin type IV and 2 in skin type V. Regarding the sun exposure time (10am to 4pm), there was 46.67±11.127 ranging from 30 min- 60 min. Moreover, all participants have no underlying disease, hypersensitivity as well as a drug allergy. In term of the drug history, 10 volunteers took supplements while other 5 did not take any medications.

5.1 Mean Melanin Index Results of Right Side of Infraorbital Area that Applied 5% Niacinamide Cream Evaluated by Mexameter

Table 1 Statistical analysis of melanin index score (right side) that applied 5% niacinamide cream at baseline, 4th, 8th and 12th week (n=15)

Melanin Index score right side	Mean	SD
Baseline	270.84	82.2
4th week	258.26	81.21
8th week	247.37	80.54
12th week	244.48	80.75
(Repeated measurement ANOVA) F=32.696, p < 0.0001		

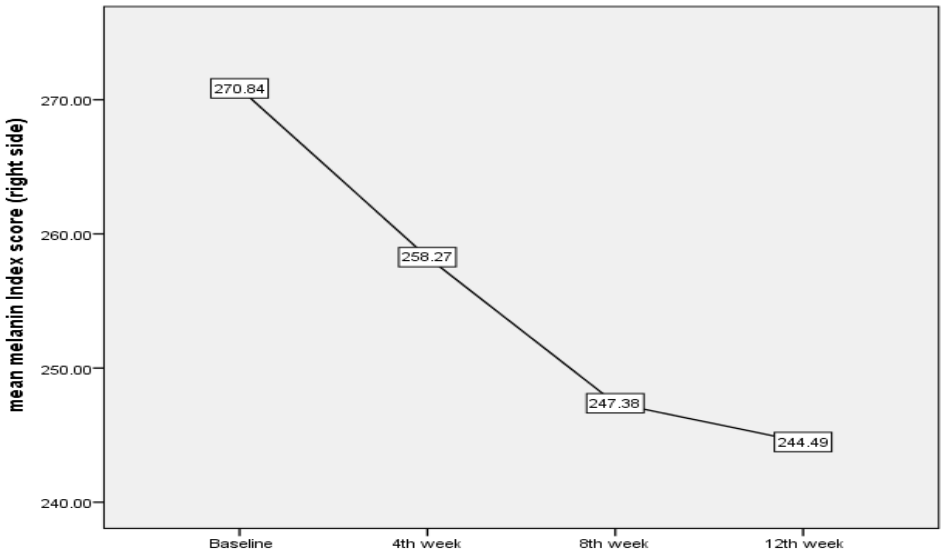

Figure 2 Line graph showing mean melanin index scores (right side) at baseline, follow-up visits 4th, 8th, and 12th week

According to the statistical analysis results, the reduction of mean melanin index score at the right side of the infraorbital area that applied 5% Niacinamide cream at baseline from 270.8 ± 82.2 (baseline) to 258.26 ± 81.21 (4th week), 247.37 ± 80.54 (8th week), and 244.48 ± 80.75 (12th week). The mean melanin index score in each visit statistically significant decreased at the level of ($p<0.0001$).

Table 2 Multiple comparison of melanin index scores (right side) at baseline, follow-up visits on 4th, 8th and 12th week

		Mean difference	Lower 95% CI	Upper 95% CI	t	p
Baseline	4th week	12.57±10.74	6.62	18.53	4.532	<0.0001
	8th week	23.46±18.32	13.32	33.61	4.961	<0.0001
	12th week	26.35±11.16	20.17	32.53	9.144	<0.0001
4th week	Baseline	-12.57±10.74	-18.53	-6.62	-4.532	<0.0001
	8th week	10.88±8.71	6.06	15.716	4.837	<0.0001
	12th week	13.77±7.09	9.84	17.7	7.521	<0.0001
8th week	Baseline	-23.46±18.32	-33.61	-13.32	-4.961	<0.0001
	4th week	-10.88±8.71	-15.71	-6.06	-4.837	<0.0001
	12th week	2.8±9.32	-2.2	8.05	1.19	0.25
12th week	Baseline	-26.35±11.16	-32.53	-20.17	-9.14	<0.0001
	4th week	-13.77±7.09	-17.7	-9.84	-7.521	<0.0001
	8th week	-2.88±9.32	-8.05	2.27	-1.199	0.25

Note Multiple comparison determines by the paired t test

The mean difference is significant at the 0.05 level.

According to multiple comparison result from table 4.3, the reduction of mean melanin index score at baseline was lower than follow up 4th week (12.57) and 8th week (23.46) and 12th week (26.35) statistically significant at the level of 0.05 ($p<0.05$). Additionally, the Mexameter score follow up 4th week and 8th week is significantly different ($p<0.0001$)

5.2 Mean Melanin Index Results of Left Side of Infraorbital Area that Applied 5% Niacinamide Cream Evaluated by Mexameter

Table 3 Statistical analysis of melanin index score (left side) that applied 5% niacinamide cream at baseline, 4th, 8th and 12th week (n=15)

Melanin Index score left side	Mean	SD
Baseline	263.02	83.56
4th week	249.68	80.06
8th week	243.64	79.12
12th week	240.86	83.34
(Repeated measurement ANOVA) F=22.453, p <0.0001		

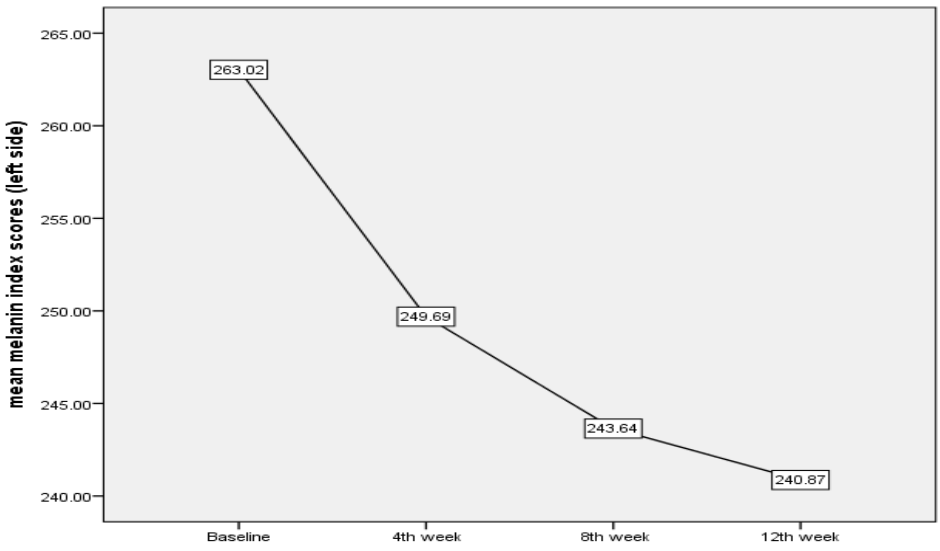

Figure 3 Line graph showing mean melanin index scores (left side) at baseline, follow-up visits 4th, 8th, and 12th week

According to the statistical analysis results, the reduction of mean melanin index score at the left side of the infraorbital area that applied 5% Niacinamide cream at baseline from 263.02 ± 83.56 (baseline) to 249.68 ± 80.06 (4th week), 243.64 ± 79.12 (8th week), and 240.86 ± 83.34 (12th week). The mean melanin index score in each visit statistically significant decreased at the level of ($p<0.0001$).

Table 4 Multiple comparison of melanin index scores (left) at baseline, follow-up visits 4th, 8th and 12th week after last treatment sessions

		Mean difference±SD	Lower 95% CI	Upper 95% CI	t	p
Baseline	4th week	13.33±16.28	4.31	22.35	3.172	.007
	8th week	19.37±13.98	11.63	27.12	5.367	<0.0001
	12th week	22.15±8.48	17.46	26.85	10.119	<0.0001
4th week	Baseline	-13.33±16.28	-22.35	-4.31	-3.172	.007
	8th week	6.04±4.26	3.68	8.4	5.492	<0.0001
	12th week	8.82±11.77	2.3	15.34	2.901	.012
8th week	Baseline	-19.37±13.98	-27.12	-11.63	-5.36	.000
	4th week	-6.04±4.26	-8.4	-3.68	-5.49	.000
	12th week	2.77±9.47	-2.46774	8.02507	1.136	.275
12th week	Baseline	-22.15±8.48	-26.85	-17.46	-10.119	.000
	4th week	-8.82±11.77	-15.34	-2.3	-2.901	.012
	8th week	-2.77±9.47	-8.02	2.46	-1.136	.275

Note Multiple comparison determine by the paired t test
The mean difference is significant at the 0.05 level.

According to multiple comparison result from table 4.3. the reduction of mean melanin index score for left side of the infraorbital area at baseline was lower than follow up 4th week (13.33) and 8th week (19.37) and 12th week (22.15) statistically significant at the level of 0.05 ($p<0.05$). Additionally, the mexameter score follow up 8th week and 12th week is significantly different ($p=<0.0001$)

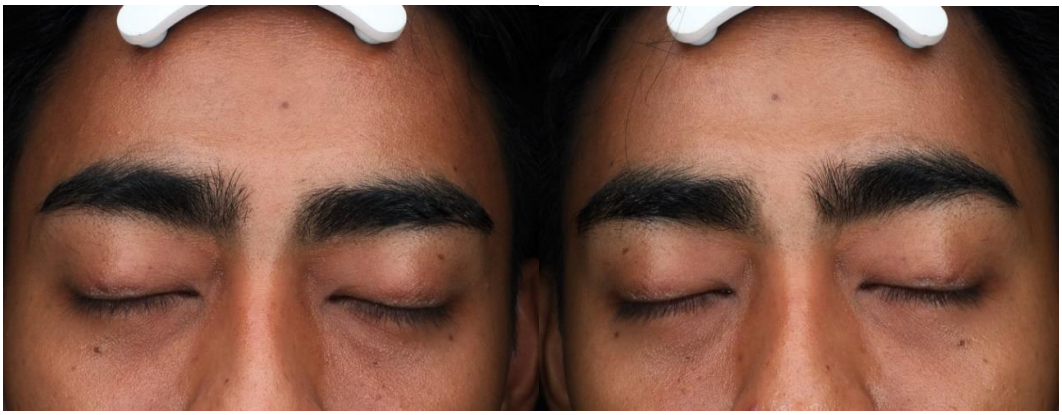

Figure 4 Before (left) and after (right) of infraorbital hyperpigmentation by applying 5% niacinamide cream

5.3 Dermatologists' satisfactory and Patient Satisfactory Score

Table 5 Statistical analysis of dermatologists' satisfaction score of 5% niacinamide cream in infraorbital area on follow-up 4th, 8th, and 12th week

	Dermatologists' satisfaction			
	25%= fair improvement	**50%=moderate improvement**	**75%= good improvement**	**100%=excellent improvement**
	n (%)			
4th week	2(13.3%)	13(86.7%)	-	-
8th week	2(13.3%)	3(20%)	10(66.7%)	-
12th week	-	1(6.7%)	2(13.3%)	12(80%)

As shown in table 4.8, 5% Niacinamide cream was applied on 4th week, dermatologist evaluation for both sides of the eyes showed 86.7% as moderately improved in 13 volunteers and 13.3% of fairly improved in 2 volunteers. On 8th week of evaluation, there was more improvement than 4th week showing 10 participants (66.7%) as good improvement. 3 (20%) and 2 (13.3%) participants were evaluated as moderate and fair improvement respectively. Furthermore, on the 12th week follow-up visit, there were 12(80%) volunteers as excellent improvement and 2(13.3%) as good improvement and 1(6.7%) as moderate improvement.

Table 6 Statistical analysis of participants' satisfaction score of 5% niacinamide cream in infraorbital area on 12th week follow-up

Patient satisfaction at 12 week	**n**	**%**
Excellent improvement (100%)	10	67
Good improvement (75%)	4	27
Moderate improvement (50%)	1	7

According to Table 4.9, participants rate the satisfactory score on 12th week visit in which 10 volunteers rated as excellent progress, 4 volunteers as good progress and 1 as moderate progress.

5.4 Adverse Effect

During the study, no adverse effect was noted in all participants after applying with 5% Niacinamide cream to infraorbital area.

6. Discussion

Nowadays, infraorbital hyperpigmentation is a common dermatological condition, and it can highly affect on the person' confidence looking fatigued and less youthful appearance. Therefore, people are looking forward to an effective treatment for this. New therapeutic options are forthcoming ranging from various topical uses, injections and laser based procedures (Friedmann & Goldman, 2015). Among them, topical cream of 5% Niacinamide is less expensive and more effective to use as whitening agent around the eye.

Niacinamide, a biologically active form of vitamin B3, is a water-soluble vitamin that is not stored in our body. Regarding the mechanism of action of niacinamide on hyperpigmentation, niacinamide affects on the cytokine signaling pathway to and from keratinocyte in which melanogenesis is stimulated by elevated endothelin-1 from keratinocytes, being triggered to release by UV-induced interleukin-1 in epidermis (Imokawa et al., 1995). Another action is that it can modulate the protease-activated receptor 2 activation in keratinocyte which interfere with phagocytosis, affecting the melanosome transfer (Seiberg, 2001). Moreover, there are many properties of niacinamide such as anti-inflammatory effect by decreasing interleukin 8 secretion and inhibiting PARP-1 , moisturizing effect by decreasing transepidermal water loss (Chen & Damian, 2014).

In previous study, the effect of 5% Niacinamide cream on reducing facial pigmentation was observed by comparing with vehicle cream for 8 weeks duration. The result revealed a significant reduction in facial hyperpigmentation on the side of using niacinamide cream (Hakozaki et al., 2002). In another study, the effect of 5% Niacinamide cream on aging skin was conducted by comparing with placebo for 12 weeks. The outcome showed that there was improvement in the appearance of facial skin texture, wrinkle as well as hyperpigmentation (Hakozaki et al., 2002).

The major aim of this study is to conduct the efficacy and adverse effect of 5% Niacinamide cream for infraorbital hyperpigmentation. To our knowledge, this is a clinical experimental study to investigate the efficacy, satisfaction, and adverse effects of 5% Niacinamide cream for infraorbital hyperpigmentation.

The study was done in Mae Fah Luang Hospital, Bangkok and measured the results by Mexameter MX at 0, 4, 8, 12 weeks interval. At the end of the research, the satisfaction score by 3 dermatologists and participants were noted. A total 15 volunteers with the Fitzpatrick skin type 3, 4 and 5 with infraorbital hyperpigmentation were participated and all the volunteers were completed in this study. In term of gender, 12 female and 3 male subjects were joined in this research. The mean age of the volunteers was 28.4 ± 2.1 ranging from 25-35 years in which there were 12 students and 3 employers working in an office. All participants had an eye cream usage history before but there was no history of treatment procedures around the undereye areas recently. Regarding the skin phenotype, 2 people of skin type 3, 11 people of skin type 4 and 2 people of skin type 5 were conducted in this study. Moreover, none of the volunteer had an allergy history. There was no history of underlying medical diseases.

The results of the study showed that there was a statistically significant melanin concentration reduction from baseline period. The decreasing of mean melanin index of 5% Niacinamide may be caused by reducing melanin transfer and contains significant antioxidant and anti-inflammatory actions.

At 12th week, for dermatologists grading, excellent progress in 12 participants, good improvement in 2 participants, moderate improvement in 1 participant with 5% Niacinamide cram application. In term of patient satisfaction, all participants would suggest using 5% Niacinamide cream to their relatives and friends. According to the adverse effects, using 5% Niacinamide cream around the infraorbital areas showed no significant adverse effects during the study period and was well tolerated and safe; accordingly, it could be used for longer periods. However, further studies are necessary to evaluate the combination of this topical cream with other agents and procedure in the treatment of infraorbital hyperpigmentation.

7. Suggestion

(1) The finding from this study may be used as an alternative treatment for infraorbital hyperpigmentation and the collected data may be used in comparison with other topical whitening agent around the under-eye area**.**

(2) Niacinamide may have benefits in other aesthetic conditions and purposes. Thus, this may be used as a reference for the treatment of inflammatory acne and dermatological skin conditions.

8. Acknowledgement

I would like to take this opportunity to express my gratitude to all those who kindly cooperated in the completion of the thesis. My first must go to supervisor, Dr. Tanomkit Pawcsuntorn, M. D., Lecturer and for his support, suggestion, and valuable guidance throughout this study.

I want to express my graditude to Prof. Dr. Thamthiwat Nararatwanchai for his advice throughout the research. I would like to thank to Assoc. Prof. Wongdyan Pandii for giving me valuable comments on the thesis.

I would like to show my appreciation to all my seniors for their sincere help and support all these years. Thanks to the volunteers who participated in this research. I want to express my special recognition to all my colleague and classmates for help and advice. I would like to express my special gratitude to my parents supporting me financially and mentally during my stressful situation.

Finally, I would like to thank to the whole team of publisher and everyone for helping and supporting and participating throughout my research journey.

10. References

Bissett, D. L., Miyamoto, K., Sun, P., Li, J., & Berge, C. A. (2004). Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin1. **International Journal of Cosmetic Science,** *26*(5); 231–238. https://doi.org/10.1111/j.1467-2494.2004.00228.

Bissett, D. L., Robinson, L. R., Raleigh, P. S., Miyamoto, K., Hakozaki, T., Li, J., & Kelm, G. R. (2009). Reduction in the appearance of facial hyperpigmentation by topical N -undecyl-10-enoyl-l-phenylalanine and its combination with niacinamide. **Journal of Cosmetic Dermatology,** 8(4); 260–266. https://doi.org/10.1111/j.1473-2165.2009.00470.

Chaidemenos, G. C. (2001). Tetracycline and niacinamide in the treatment of blistering skin diseases. **Clinics in Dermatology,** 19(6); 781–785. https://doi.org/10.1016/S0738-081X(00)00187-5.

Chen, A. C., & Damian, D. L. (2014). Nicotinamide and the skin: Nicotinamide and the skin. **Australasian Journal of Dermatology,** 55(3); 169–175. https://doi.org/10.1111/ajd.12163.

Friedmann, D. P., & Goldman, M. P. (2015). Dark Circles. **Clinics in Plastic Surgery,** 42(1); 33–50. https://doi.org/10.1016/j.cps.2014.08.007.

Hakozaki, T., Minwalla, L., Zhuang, J., Chhoa, M., Matsubara, A., Miyamoto, K., Greatens, A., Hillebrand, G. G., Bissett, D. L., & Boissy, R. E. (2002). The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. **British Journal of Dermatology,** 147(1); 20–31. https://doi.org/10.1046/j.1365-2133.2002.04834.

Imokawa, G., Miyagishi, M., & Yada, Y. (1995). Endothelin-1 as a New Melanogen: Coordinated Expression of Its Gene and the Tyrosinase Gene in UVB-Exposed Human Epidermis. **Journal of Investigative Dermatology,** 105(1); 32–37. https://doi.org/10.1111/1523-1747.ep12312500.

Lee, D. H., Oh, I. Y., Koo, K. T., Suk, J. M., Jung, S. W., Park, J. O., Kim, B. J., & Choi, Y. M. (2014). Reduction in facial hyperpigmentation after treatment with a combination of topical niacinamide and tranexamic acid: A randomized, double-blind, vehicle-controlled trial. **Skin Research and Technology,** 20(2); 208–212. https://doi.org/10.1111/srt.12107.

Nayak, C. S., Ansari, S. M. M., Salve, V., & Patil, S. (2019). Effectiveness of a combination of anti-pigmentary products in facial post-inflammatory hyperpigmentation. **International Journal of Research in Dermatology,** 6(1), 1. https://doi.org/10.18203/issn.2455-4529. IntJResDermatol20195199.

Rolfe, H. M. (2014). A review of nicotinamide: Treatment of skin diseases and potential side effects. **Journal of Cosmetic Dermatology,** 13(4); 324–328. https://doi.org/10.1111/jocd.12119.

Sawant, O., & Khan, T. (2020). Management of periorbital hyperpigmentation: An overview of nature‐based agents and alternative approaches. **Dermatologic Therapy,** 33(4). https://doi.org/10.1111/dth.13717

Seiberg, M. (2001). Keratinocyte-Melanocyte Interactions During Melanosome Transfer: Melanosome Transfer. **Pigment Cell Research,** 14(4); 236–242. https://doi.org/10.1034/j.1600-0749.2001.140402.

Surjana, D., Halliday, G. M., Martin, A. J., Moloney, F. J., & Damian, D. L. (2012). Oral Nicotinamide Reduces Actinic Keratoses in Phase II Double-Blinded Randomized Controlled Trials. **Journal of Investigative Dermatology,** 132(5); 1497–1500. https://doi.org/10.1038/jid.2011.459.

Wohlrab, J., & Kreft, D. (2014). Niacinamide—Mechanisms of Action and Its Topical Use in Dermatology. **Skin Pharmacology and Physiology,** 27(6); 311–315. https://doi.org/10.1159/000359974.