CLINICAL COMPARISON BETWEEN TOPICAL 2.5%BENZOYL PEROXIDE + 5% NIACINAMIDE AND 2.5%BENZOYL PEROXIDE IN THE TREATMENT OF MILD TO MODERATE FACIAL ACNE VULGARIS

By

MISS TARNYAMAS KAEWSANIT

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (DERMATOLOGY) CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE THAMMASAT UNIVERSITY

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was approved as partial fulfillment of the requirements for

the degree of Master of Science (Dermatology)

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Thesis Title	CLINICAL COMPARISON BETWEEN TOPICAL 2.5% BENZOYL PEROXIDE + 5% NIACINAMIDE AND 2.5% BENZOYL PEROXIDE IN THE TREATMENT OF MILD TO MODERATE FACIAL ACNE VULGARIS
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ABSTRACT

Acne vulgaris is a common multifactorial inflammatory disease affecting the pilosebaceous units of the skin found commonly in dermatology outpatient departments. The major pathogenic factors involved are increased sebum production, follicular hyperkeratinization which leads to obstruction of sebaceous follicles, colonization of pilosebaceous units by *Propionibacterium acnes*, and perifollicular inflammation. An old and well-known topical treatment is benzoyl peroxide, which is an antibacterial agent that kills *Propionibacterium acnes* through the release of free oxygen radicals and it is also mildly comedolytic. When combined with a new topical therapy, topical niacinamide, which is an amide of vitamin B-3 and has an anti-inflammatory effect, reduces facial sebum production, and it also has a skin lightening effect. This combined treatment can lead to better efficacy in the treatment of facial acne vulgaris. Further, it can also help in post acne erythema and post inflammatory hyperpigmentation.

The present study aims to investigate the efficacy of a new topical drug combined with an old topical therapy (5% niacinamide plus 2.5% benzoyl peroxide) in patients with acne vulgaris. The study also seeks to observe the side effects of this combination. Seventeen patients with mild to moderate acne vulgaris were included in the study, with

a mean age of 26. The study was a randomized, intraindividual, double-blinded controlled trial. The treatment was randomly assigned to the left or the right side of the face for individual participants. One side received topical 2.5% benzoyl peroxide + 5% niacinamide, while the other side received only topical 2.5% benzoyl peroxide for a period of 12 weeks. The efficacy was evaluated by using lesion counts, sebum casual level by Sebumeter®, post acne erythema, and post inflammatory hyperpigmentation by ANTERA3D camera®. At week 12, the niacinamide group (5% niacinamide + 2.5% benzoyl peroxide) showed significant reductions to both acne lesion count and sebum casual levels from the baseline (p=0.000 and p=0.001, respectively). The reduction of non-inflammatory lesions count in the niacinamide group was better than the cream base group (2.5% benzoyl peroxide + cream base) with a statistically significant difference (p=0.004). Yet the reduction of inflammatory lesions was not significantly different between the two groups. Interestingly, the sebum casual level in the niacinamide group reduced faster than for the cream base group. The post acne erythema score reduced from the baseline for both groups with no statistically significant difference within and between the two groups. The post inflammatory hyperpigmentation scores from acne showed increases for both groups above the baseline with a statistically significant difference in the cream base group (p = 0.000) and not significant difference in the niacinamide group (p = 0.58), but there was no statistically significant difference between the two groups. Furthermore, there were no statistically significant differences found between the two groups at every follow-up visit in terms of physician improvement scale, patient satisfaction index, and side effects.

The combination of 2.5% benzoyl peroxide with 5% niacinamide is found to be more effective in the treatment of mild to moderate facial acne vulgaris, since it was found to reduce non-inflammatory lesions and more quickly improve non-inflammatory lesions and facial sebum reduction compared to 2.5% benzoyl peroxide with a cream base. It also had minimal side effects. However, the efficacy of 2.5% benzoyl peroxide with 5% niacinamide at treating inflammatory lesions, post acne erythema, and post-inflammatory hyperpigmentation is comparable to 2.5% benzoyl peroxide with a cream base.

Keywords: Niacinamide, benzoyl peroxide, acne vulgaris, treatment

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Miss Tarnyamas Kaewsanit

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LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
AD	atopic dermatitis
AK	actinic keratosis
ATP	adenosine triphosphate
BP	benzoyl peroxide
COCs	Combined oral contraceptive pills
DHT	dihydrotestosterone
DHEA	dehydroepiandrosterone
HSD	3β -hydroxysteroid dehydrogenase
IL	interleukin
KTP	potassium titanyl phosphate
MAPK	mitogen activated protein kinase
MHC	major histocompatibility complex
MTX	methotrexate
NAD	nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NFκB	nuclear factor kappa B
NMSC	non-melanoma skin cancer
PDT	photodynamic therapy
PPAR	peroxisome proliferator-activated receptors
TEWL	transepidermal water loss
TLR	toll-like receptor
TNF	tumor necrosis factor
TMP/SMX	trimethoprim/sulfamethoxazole
UV	ultraviolet

CHAPTER 1
INTRODUCTION

Acne vulgaris is an inflammatory disorder caused by many factors and affecting the pilosebaceous units of the skin found commonly in dermatologic outpatient department. The main pathogenic factors are increasing in sebum production, follicular hyperkeratinization which leads to obstruction of sebaceous follicles, *Propionibacterium acnes* colonization in pilosebaceous units and inflammation around the follicles. The clinical presentation of acne vulgaris ranges from mild comedones to severe pustules and cysts.[1]

The topical therapy for acne vulgaris includes the usage of many agents as monotherapy or combined. Commonly used topical acne therapies include benzoyl peroxide, retinoid, antibiotics, salicylic acid, azelaic acid, dapsone, combination antibiotics with benzoyl peroxide, retinoid with benzoyl peroxide and retinoid with antibiotic. Therapeutic decisions may depend on patients' age, area of involvement, and severity of disease, and patient preference. In treatment of mild to moderate acne vulgaris, recommendations based on Guidelines of care for the management of acne vulgaris from the American Academy of dermatology are topical combination therapy.[2]

Benzoyl peroxide is an antibacterial drug. It releases free oxygen radicals that can kill *P. acnes* and also has mild comedolytic effect.[3, 4] At present, there is still no report about drug resistance. Combination of BP with topical antibiotic treatment makes better results and may reduce development of antibiotic resistance. Benzoyl peroxide has some side effects including irritation with concentration-dependence, staining and bleaching of clothes, and uncommon allergic contact dermatitis.

Topical Niacinamide or nicotinamide is an amide of vitaminB3(niacin) which has anti-inflammatory effect [5] , reduce facial sebum production[6] and also lightening effect [7-9] . It is widely used in cosmetic preparations and considered safe up to 5%[10].

This study compared between combination of 2.5% benzoyl peroxide plus 5% Niacinamide and 2.5% benzoyl peroxide plus cream base in the treatment of acne

vulgaris. We aim to find if 5% Niacinamide is an effective drug to be added for better treatment result in mild to moderate acne vulgaris.

CHAPTER 2
REVIEW LITERATURE

2.1 Review of acne vulgaris

2.1.1 Epidemiology

Acne is a common chronic inflammatory skin disorder. It can be seen in mild degrees since baby born. This probably results from follicular stimulation by maternal hormones. However, it is not a significant problem until puberty. Acne often occurs in the puberty age. Acne prevalence peak is during the middle to late teenage period. More than 85% of adolescents are affected. It gradually decreases at older. However, acne may persist through adult period, particularly in women.

2.1.2 Pathogenesis

There are a number of factors leading to the onset of acne, but the basic process involves four steps[1]. The main factors can be explained as follows:

2.1.2.1 Follicular epidermal hyperproliferation

A microcomedo is the consequence of follicular epidermal hyperproliferation. As the epithelium of the infundibulum becomes hyperkeratotic as the keratinocytes show enhanced cohesion, excess cells are the result, and their adhesive nature causes them to form a plug which blocks the follicular ostium. As a result, there is a gradual accumulation of sebum, keratin, and bacteria in the follicle which causes a microcomedo to form as the upper hair follicle dilates. It is not yet understood what causes this keratinocyte hyperproliferation along with heightened adhesion, but some of the factors which have been suggested as underlying causes include lower levels of linoleic acid, androgen stimulation, enhanced interleukin-1 (IL-1) activity, and the effects of *Propionibacterium acnes.*

One highly potent androgen which might be responsible for acne is dihydrotestosterone (DHT). Alternatively, a weaker androgen is dehydroepiandrosterone (DHEA), which can be converted to Androstenedione through the action of 3β-hydroxysteroid dehydrogenase (HSD), while 17 β-HSD then converts Androstenedione to testosterone before 5-α reductase converts this testosterone to

dihydrotestosterone (DHT), which is the major hormonal effector located on the sebaceous gland. Infra-infundibular keratinocytes contain more 17 β-HSD and 5-α reductase in comparison to epidermal keratinocytes, and this is the main reason why there is greater production of DHT around the follicles. It is possible that DHT is an active contributor to follicular hyperkeratinization in acne.[11, 12]

Meanwhile, linoleic acid is an essential fatty acid found in the skin which occurs in lower quantities in acne patients, and thus it is proposed that linoleic acid might be a regulator of the proliferation of follicular keratinocytes. When levels of linoleic acid fall below normal, this can trigger the hyperproliferation of follicular keratinocytes, leading to the production of proinflammatory cytokines. Some researchers have claimed that in such scenarios, the levels of linoleic acid production are in fact normal, but the additional sebum which is produced serves to dilute the acid. It is thought that IL-1 α may serve as one of the stimuli in keratinocyte hyperproliferation. For *in vitro* studies, hyperproliferation and microcomedone creation have been demonstrated by human follicular keratinocytes following the addition of IL-1 α. IL-1 receptor antagonists can restrict the formation of microcomedones *in vitro*[13], thereby adding supporting evidence for the role of cytokines in the pathogenesis of acne.[1]

2.1.2.2 Excess sebum production

Acne patients produce greater quantities of sebum than normal, healthy individuals. Sebum contains lipoperoxides which result from the peroxidation of squalene in combination with reduced levels of vitamin E. It is these lipoperoxides which might be responsible for increased sebum production, since they produce proinflammatory cytokines and also activate the peroxisome proliferator-activated receptors (PPAR) pathway, which is the step which is required in order to generate increased levels of sebum[14]. Another mechanism by which sebum production is increased is by the action of androgenic hormones upon sebocyte proliferation and differentiation. Meanwhile, androgen hormones can bind to sebocytes and influence their activity in a manner similar to that of follicular infundibular keratinocytes as previously described [1]

2.1.2.3 Inflammation

Having formed, the microcomedo can continue its expansion as more keratin, sebum, and bacteria become densely packed. Eventually, the result is the rupture of the follicular wall, releasing the keratin, sebum, and bacteria into the dermis. Inflammation is the response to this sequence of events. Triglycerides, which are a component of sebum, can then be broken down to form free fatty acids by Propionibacterium acnes, which is typically found in the pilosebaceous unit. Bacterial clumping can be promoted by these free fatty acids, allowing colonization by Propionibacterium acnes, which thus stimulates further inflammation [1].

2.1.2.4 The presence and action of *Propionibacterium acnes*

Propionibacterium acnes is a gram-positive, anaerobic, and microaerobic bacterium which lives in a biofilm inside the pilosebaceous unit. They form communities which reside within a casing created from an extracellular polysaccharide lining which is secreted by the bacteria once they have attached themselves to the surface. The resulting gylcocalyx polymer acts as a physical obstacle, preventing antimicrobial concentrations from reaching effective levels within the microenvironment of the biofilm. P. acnes secretes the gylcocalyx polymer to serve as a biofilm, but this can result in antibiotic resistance because the polymer is influential in the inflammation process. [15]

P. acnes cell walls contain carbohydrate antigens which can stimulate patients to generate antibodies, which in turn trigger a cascade of pro-inflammatory processes which promote an even stronger inflammatory response[16]. P. acnes is capable of producing proteases, lipases, hyaluronidases, and other chemotactic factors which can elicit a delayed kind of hypersensitivity response. All of these factors serve to increase inflammation [17].

Furthermore, P. acnes will bind to the toll-like receptor 2 (TLR-2) on both the monocytes and polymorphonuclear cells which are located around the sebaceous follicle. This causes the release of a number of proinflammatory cytokines including IL-1 α, IL-8, IL-12, and TNF-α [18, 19].

The antimicrobial peptides, Histone H4 along with cathelicidin, are also secreted as a response to the presence of P. acnes, and these will serve to kill microbes directly, as well as acting is support of the innate immune system

through β defensins and psoriasin [20, 21].

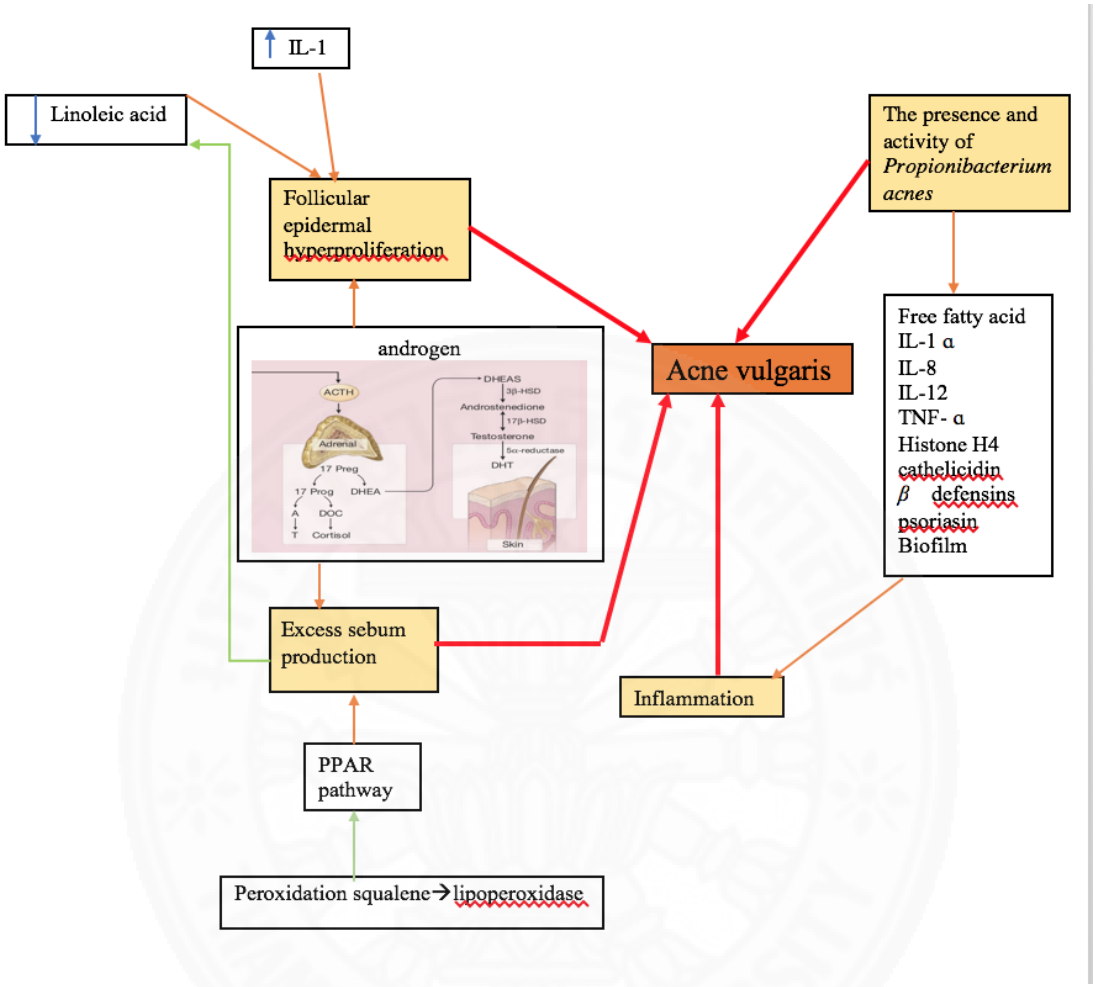


Figure 2.1 Acne pathogenesis

2.1.3 Guideline Management of Acne vulgaris

According to Guidelines of care for the management of acne vulgaris from Jounal of American Academic of Dermatology 2016, the management of acne vulgaris [2] depends on the severity of acne as shown in Table 1 But nowsday, there is no universally agreed-upon grading system. It can differ in each dermotologist's opinion. In this study will use the Global Acne Grading System(GAGS) because it has shown to be better than acne grading system in accuracy, less time consuming and minimalization of inter- and intra-grader variability [22]

Table 2.1 Acne vulgaris treatment from Goldsmith, L.A., Fitzpatrick's Dermatology in General Medicine 8th Edition. 2012. 8th edition: p. 897-917.

	mild	Moderate	severe
1st line treatment	Benzoyl Peroxide(BP) or Topical retinoid or Topical combination therapy: BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical combination therapy: BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic or Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral antibiotic + Topical Combination therapy: BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic or Oral Isotretinoin
Alternative	Add topical Retinoid or BP (if not on already) or Consider Alternate Retinoid or Consider	Consider Alternate Combination Therapy or Consider Change in Oral Antibiotic or Add Combined Oral	Consider Change in Oral Antibiotic or Add Combined Oral Contraceptive or Oral Spironolactone(Females) or Consider Oral Isotretinoin

	Topical Dapsone	Contraceptive or Oral Spironolactone (Females) or Consider Oral Isotretinoin	

2.1.3.1 Topical therapy

In cases where the acne symptoms are mild to moderate, treatment usually begins with topical therapy, often involving benzoyl peroxide (BP), salicylic acid, antibiotics, combinations of antibiotics with BP, retinoids, retinoids with antibiotics, retinoids with BP, azelaic acid, and sulfone agents.

Benzoyl peroxide or BP is an antibacterial drug which is capable of killing P. acnes by releasing free oxygen radicals. It is also reported to have a mild comedolytic effect. The main benefit of BP is that to date there is no resistance to its activity, and therefore it can be combined with other topical antibiotics to provide enhanced results, while simultaneously ensuring that any development of resistance is reduced. BP can be applied as a topical wash, cream, gel, or foam, and can take the form of both wash-off or leave-on treatments. The available strengths when it is used to treat acne are in the range of 2.5% up to 10%. The main drawbacks to its use are that it can cause irritation, depending on the concentration used, can lead to rare contact allergies, and will stain fabrics.

Common topical antibiotics include clindamycin and erythromycin, which are antibacterial agents which also have anti-inflammatory properties.[23] Combining these drugs with BP makes the treatment more effective, and lowers the chance of developing bacterial resistance. The most frequently reported side effects are diarrhea or colitis caused by Clostridium difficile.[24] Meanwhile, clindamycin is rated as category B for pregnancy.

Topical retinoids are vitamin A derivatives. There are three available forms: tretinoin, adapalene and tazarotene. Retinoids are the mainstay of topical therapy for acne. Their mechanisms are comedolytic and anti-inflammation that can help resolve the precursor microcomedone lesion. Recently there is a study found that topical retinoic acid can also reduce facial sebum production. [25] Their side effects for example dryness, peeling, erythema, and irritation make them limited usage. Topical retinoids increase risk of photosensitivity so the patient should use daily sunscreen to reduce the risk of sunburn. [2] moreover, they are embryotoxic agent.[26]

Azelaic acid 20% is used as a topical therapy which has comedolytic, antibacterial, and anti-inflammatory properties and is mildly effective. It is especially helpful in patients who have dark skin because it has a lightening effect when dyspigmentation occurs.[27-29] Azelaic acid is category B in pregnancy.

Sulfone agents such as dapsone 5% gel have been proved to offer mild to moderate effectiveness when inflammatory lesions must be reduced, but it is not known exactly how the process develops[30, 31]. It is believed that the anti-inflammatory effects result from the inhibition of neutrophil myeloperoxidase, eosinophil peroxidase, and chemoattractant-induced signal transduction[32]. It appears more effective in female patients than in males or adolescents.[33, 34] When BP is added to topical dapsone, the outcome can be an orange-brown skin coloration, although this can readily be washed away. Topical dapsone 5% gel can be classified as category C for pregnancy.

Salicylic acid is a comedolytic agent mostly used as a chemical peel at dermatologist clinic but the clinical trial using salicylic acid as a topical therapy at patients' home in acne treatment is scanty.

2.1.3.2 Systemic antibiotics[2]

Systemic antibiotics have traditionally played a major role in treating acne cases which are moderate to severe. Ideally, they should be combined with topical therapy to be most effective. Empirical evidence indicates that tetracycline, minocycline, doxycycline, amoxicillin, erythromycin, azithromycin, cephalexin, trimethoprim/sulfamethoxazole (TMP/SMX) and trimethoprim are all effective in this role.[2, 35-38]

Tetracycline class drugs are the principal treatment approach for moderate to severe acne, with the exception of cases where the patient is pregnant, aged below eight years, or has an allergy to the specific drugs involved. It works by restricting the synthesis of protein through the binding of the 30S subunit of the bacterial ribosome, while its anti-inflammatory properties serve to limit chemotaxis and metalloproteinase activity. Examples of drugs are doxycycline, minocycline.

Erythromycin and azithromycin are alternative drugs when traditional antibiotics are contraindicated. It binds the 50S subunit of the bacterial ribosome and also has some anti-inflammatory properties

TMP/SMX have also been used for the treatment of acne. These 2 agents work synergistic to block nucleotide and amino acid synthesis in the bacteria

Penicillins and cephalosporins are sometimes used in acne treatment for example in pregnant women

2.1.3.3 Hormonal agents

COCs (Combined Oral Contraceptives) are taken in the form of pills which contain both estrogen and progestin. Their action in treating acne relies upon their antiandrogenic effect. Those COCs which have received FDA approval for acne treatment do so on the condition that it is made clear that it can be used for female patients who also require contraception. The use of COCs has been linked to increased cardiovascular risks, a heightened risk of breast cancer, and VTEs (Venous Thromboembolic Events). [39]

Another hormonal agent is spironolactone, which is an aldosterone receptor antagonist. It offers a high level of potency in terms of antiandrogen activity through the reduction of testosterone production and by competitively restricting the binding of testosterone and dihydrotestosterone to the androgen receptors located in the skin. [40] The recent Cochrane database review determined a lack of sufficient evidence to demonstrate the efficacy of spironolactone as a suitable treatment option for acne patients. [41] However, despite the absence of published data, some evidence does exist, supported by expert opinion, that spironolactone can be used to manage acne in selected women. [2]

2.1.3.4 Isotretinoin

Patients suffering severe acne may use oral isotretinoin, which is an isomer of retinoic acid. Its effect is to reduce sebum production, as well as improving the condition of acne lesions and acne scarring. It can also help to reduce the symptoms of stress or depression which are associated with moderate yet treatment-resistant acne, [42, 43] and can be used when patients suffer a relapse immediately after ceasing a course of oral antibiotic therapy. [44]

2.1.3.5 Other therapies and physical modalities

(1) Comedo removal: it has been used for long time with limited evidence published. Expert opinions agreed that comedone removal is often helpful in the management of comedonal acne that cannot be removed by other treatment.

(2) Chemical peels: Glycolic acid and salicylic acid chemical peels may be helpful for comedones but require multiple treatments and the results are not permanent[45-48].

(3) Laser and light devices

Laser: pulsed dye laser, potassium titanyl phosphate (KTP) laser, fractionated and nonfractionated infrared lasers, fractionated CO_2 laser.

Light devices: radiofrequency, intense pulsed light, photopneumatic therapy, and photodynamic therapy (PDT)

The most evidence exists for PDT in treating acne. After apply photosensitizer, light device activates the photosensitizer and generate singlet oxygen species result in damaging the sebaceous glands and reducing P acnes.[49, 50]

(4) Intralesional injection of triamcinolone acetonide : use in large, nodular acne for rapid improvement and decreasing pain.[51]

2.1.4 Alternative therapies

Herbal agents such as tea tree oil [52] and other topical drugs such as gluconolactone[53], Niacinamide [54, 55] found to be effective for the treatment of acne.

2.1.5 Diet and its effects on acne

Evidence is appearing which indicates that diets which have a high glycemic index could be linked to acne. [56, 57] Moreover, observational research studies have shown that some dairy products, and in particular skimmed milk, might serve to exacerbate acne. [58] However, further evidence is still needed to support this claim.

2.1.6 Acne and sequelae

After acne is subsided, it can result in post inflammatory erythema in fair skin type caused from wound-healing related microvascular dilatation and post inflammatory hyperpigmentation in dark skin type.[59] It can also result in scarring and psychological sequelae such as anxiety, depression, embarrassment and shame. [60]

2.2 Review of Niacinamide

2.2.1 Introduction

Niacinamide/Nicotinamide is an amide of vitamin B_3 or niacin. The structure of Niacinamide consists of a pyridine ring with an amide group in position 3 as shown in Figure 2.2. It is a hydrophilic endogenous substance and does not stored in the body. We get it by ingestion of diet containing vitamin B3 and tryptophan. Tryptophan is an essential amino acid which is found in dietary protein. Tryptophan can be converted to niacin in the liver but this is inefficient conversion. Vitamin B3 in the form of niacin or nicotinamide can be found in many foods such as chicken, pork, beef, fish, beans, mushrooms, yeast extracts and coffee. Niacinamide is absorbed in the small intestine and stored as NAD in the liver [61]. These regulate the homoeostasis of the Niacinamide in serum[62]. Niacinamide is excreted by the kidneys[63]. Different metabolites are excreted depend on the dose[64].

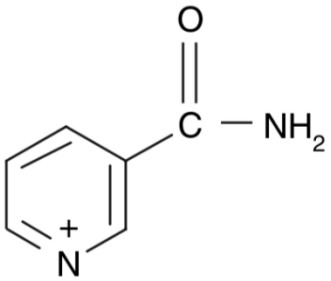


Figure 2.2 Structural formula of Niacinamide[61] from Rex, A. and H. Fink, Pharmacokinetic aspects of reduced nicotinamide adenine dinucleotide (NADH) in rats. Front Biosci, 2008. 13: p. 3735-41.

There are two forms of Niacinamide which are white crystalline powder and colorless crystals. It has a salty, bitter taste and no odor[65]. The melting point is 128-131°C, the pKa value is 3.3 (20°C) and the pH is 6.0–7.5 (β = 5 g/100 ml H_2O) [65]. Its molar weight is 122.12 g/mol [66]. Synthetic Niacinamide can be produced by 3 different methods

1. oxidation of 3-ethyl-6-methylpyridine and HNO_3 into nicotinic acid which is then transformed with NH_3 to nicotinic acid amide

2. aminolysis of methyl nicotinate and gaseous NH_3

3. ammoxidation of 3-methylpyridine into cyanpyridine and then saponified partially into nicotinamide [67-69]

Niacinamide is an important precursor of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) and their reduced high energy forms (NADH and NADPH). So it has been postulated that topical application of Niacinamide may correct local homeostatic balance of these two nucleotide coenzymes[70]

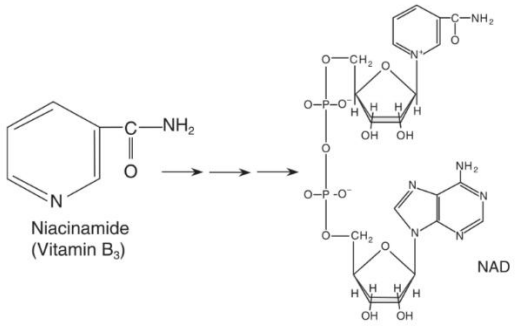


Figure 2.3 Niacinamide is a precursor to energy co-factors.[71] from Gehring, W., Nicotinic acid/niacinamide and the skin. J Cosmet Dermatol, 2004. 3(2): p. 88-93.

2.2.2 Pharmacological properties of Niacinamide with dermatologic relevance

2.2.2.1 Anti-Inflammatory Effect

Niacinamide reduce inflammation in many pathways. First is NFκB pathways, which is essential for the expression of adhesion molecules, chemokines, inflammatory cytokines and pro-inflammatory mediators. This pathway is regulated by the nuclear poly(ADP-ribose) polymerase-1 (PARP-1). And PARP-1 is inhibited by Niacinamide. [5, 72] Niacinamide can also inhibit the expression of MHC-II [73] and the production of TNF-α, IL-1,IL-6, IL-8 [5] and nitric oxide [74, 75] in vitro and animal model. Niacinamide can inhibit leucocyte chemotaxis, lysosomal enzymes release, and lymphocytes transformation. [76] Other than that, Niacinamide can inhibit IL-8 production from Propionibacterium acnes through NFκB and MAPK pathways[77]

2.2.2.2 Sebo-suppressive effect

It is theorized that Niacinamide induce the tube that connects between sebaceous gland and follicular ostium at skin surface to become exfoliated and encouraged sebum reflux to the skin surface faster leads to lack of the reservoir of sebum in the duct and possibly lead to decrease sebum excretion from the skin. As shown in a double-blinded, randomized clinical trial in 130 participants compared between 2% Niacinamide moisturizer and placebo moisturizer found that a 2% Niacinamide moisturizer significantly reduced sebum excretion rates.[6]

Another study measured sebaceous lipogenesis effect when treated with Niacinamide by using viable human biopsy tissues from face-lift surgery. The cultured biopsies were incubated with Niacinamide or trans-retinoic acid for 4 days and then incubated with 14C-acetate found that Niacinamide can reduce total lipogenesis significantly with dose-dependent manner ($p<0.01$) and the reduction from 25 mM Niacinamide was equivalent to 1uM trans-retinoic acid ($p=0.01$). Moreover, Niacinamide can reduce triglyceride remarkably when compared to control group. As triglycerides represents 50-60% of sebaceous gland lipids they conclude that Niacinamide affect lipogenesis by triglyceride reduction [70].

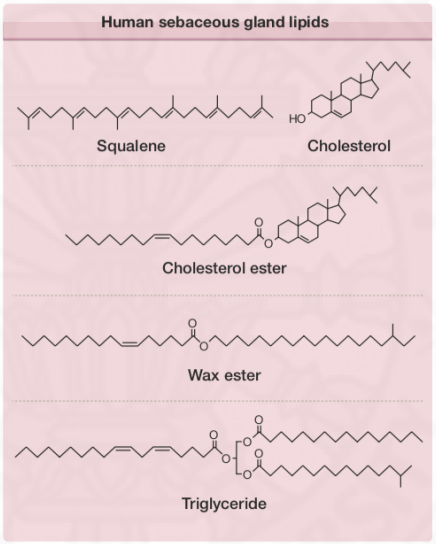


Figure 2.4 Human sebaceous gland lipids from Goldsmith, L.A., Fitzpatrick's Dermatology in General Medicine 8th Edition. 2012. 8th edition: p. 897-917.

2.2.2.3 Lightening Effect

Niacinamide is found to be related in lightening effect by the inhibition of melanosomes transfer from melanocytes to keratinocytes *in vitro* cell cocultured study.[9, 78] This makes Niacinamide different from other lightening substances such as Arbutin and Kojic acid that aim at inhibiting tyrosinase activity [79].

2.2.2.4 Antipruritic Effect

Niacinamide has a barrier-protective effects by acting on the key enzyme for the sphingolipid synthesis called “serine palmitoyltransferase”. Niacinamide activates the mRNA expression of this enzyme in the biosynthesis of ceramides in keratinocytes.[80] Due to increasing rate of ceramide synthesis, it influences stronger protection effect of the stratum corneum [81, 82] and leads to antipruritic effect. Niacinamide also inhibit cAMP-phosphodiesterase, stabilizes the mast cells and reduces histamine releasing [83-87] which can also lead to antipruritic effect.

2.2.2.5 Antimicrobial Effect

Niaciamide is tubercuolostatic by inhibition of the class III NAD-dependent deacetylase-protein family (Sir2) [88] and antiretroviral effects which is effect against HIV by inhibition of the nuclear PARP [89].There are also fungistatic effects by decreasing the activity of enzymes produced by the fungi[90]. Moreover, in vitro study found that Niacinamide inhibits P.acnes biofilm formation and increase biofilm degradation [91]

2.2.2.6 Photoprotective Effect

The photoprotective effect of Niacinamide against both photocarcinogenesis and UV-induced immunosuppression. Niacinamide against photocarcinogenesis by unblock glycolysis and replenish ATP in UV-irradiated cultured human keratinocytes[92] and also regulates PARP-1, which is main DNA repair enzyme that is activated by UV radiation. [93] For UV-induced immunosuppression, the mechanism may include alterations in complement, energy metabolism, and apoptosis[94]

2.2.3 Clinical Efficacy and clinical use of Niacinamide

Many cosmetic products widely contain Niacinamide as one of the ingredients. Several research studies report that topical Niacinamide may affect skin in many aspects. Niacinamide can be formulated easily because of its water solubility and stability when expose to light and oxygen. Furthermore, Niacinamide is also well tolerated by the skin.[95] It is considered to be safe up to a concentration of 5% [10]. However, there is a few clinical data of its efficacy and the publications available often do not indicate the preparations of the drug or the quantity for cutaneous bioavailability.

There are minor side effects were noted in some studies such as itching, burning, mild dermatitis with no significance difference from other topical drugs [96]

Study data show anti-inflammatory effects exist for atopic dermatitis [97, 98], psoriasis [97, 99, 100], rosacea[101, 102] and acne vulgaris [54, 103] but its sebostatic effect for acne vulgaris, there are still no clinical trial to demonstrate.

For the lightening effect, there are studies with Asian subjects have shown improvement of skin lightening after using a preparation containing 5% Niacinamide twice daily in the duration of 8 weeks [9].

For photoprotective effect, one study[104] evaluated the effectiveness of 1% Niacinamide emulsion compared with vehicle. The outcome was actinic keratoses lesions count during 6 months period. But there were no relevant differences.

At present, there are no clinical study to prove efficacy in antipruritic effect and antimicrobial effect yet.

2.2.3.1 Niacinamide in acne

Niacinamide was used in previous studies as a single-agent topical agent for treatment on randomized patients. Treatment involved Niacinamide only or clindamycin only, which identified that those receiving Niacinamide had considerably better acne vulgaris from baseline. Further, similar decreases in acne lesions resulted from using Niacinamide and clindamycin. [54, 55, 105] Significant decrease in acne from baseline was also found by a study that provided Niacinamide to all participants.[106] However, no study has yet compared Niacinamide to placebo-treated control participants.

Besides the previously mentioned research, Niacinamide has been employed in a blended topical product. Combined Niacinamide and clindamycin was compared to a clindamycin-only treatment group on a study, which exhibited a considerable upgrade in acne vulgaris from control for both groups. When using combined Niacinamide with clindamycin and clindamycin alone, however, no variance was found in acne vulgaris. [103]. Emulsions made of several ingredients including either 4% Niacinamide-phospholipidic (N-PHCL) emulsion, 1% clindamycin emulsion, or vehicle emulsion were used for treatment in another study of randomized patients. When compared to emulsion containing clindamycin and the emulsion

vehicle, the Niacinamide treatment group showed substantial improvement in acne vulgaris. [107] Moreover, combination therapy comprising 4% Niacinamide, 1% retinol, and 0.5% 7-dehydrocholesterol to the patient's baseline acne was carried out by another study, which showed considerable improvement in acne vulgaris from the patient's baseline. [108] It remains uncertain if the Niacinamide or other ingredients in the combination product caused the improvement in these combination treatments.

Recently, there is a preliminary in vitro study shows that Niacinamide inhibits *P.acnes* biofilm formation and increase biofilm degradation. So, Niacinamide may be a good choice for long-term acne treatment but the mechanism of antibiofilm effect is unknown and there is still no evidence in human.[91]

2.2.3.2 Niacinamide in Rosacea

Rosacea is characterized by redness of the central face with flushing, inflammatory papules, pustules, and telangiectases. [1]

There is a study investigated the efficacy of oral Nicomide (Niacinamide 750 mg + zinc 25 mg + copper 1.5 mg + folic acid 500 μg) for the treatment of acne and rosacea which is an open-label, multicenter prospective cohort study found that there was a significant improvement in the patients' self-evaluation of their condition [109]. Another study was done in 50 rosacea patients. It was an investigator-blinded observational study found that a moisturizer with Niacinamide can relieve the signs and symptoms of rosacea in 4 weeks of study, compared to no treatment group [102]. It was thought to improve skin barrier function and help with impaired skin barrier function which is involved in the pathogenesis of rosacea[110].

2.2.3.3 Niacinamide in autoimmune vesiculobullous diseases of the skin

Autoimmune vesiculobullous diseases of the skin are pemphigus which has autoantibodies directed against desmosomal structural proteins, bullous pemphigoid and epidermolysis bullosa acquisita characterized by autoantibodies directed against hemidesmosomal structural proteins, dermatitis herpetiformis that has antibodies against multiple agents such as gliadin, transglutaminase 2 and transglutaminase 3 or immunoglobulin A bullous dermatosis that has autoantibodies against basement membrane components.

The use of Niacinamide for autoimmune vesiculobullous diseases of the skin was studied mostly in bullous pemphigoid. There were only one case report suggest that oral Niacinamide as monotherapy may be an effective treatment in bullous pemphigoid[111] and some case reports suggested that combination of oral Niacinamide with tetracycline may be an effective treatment for bullous pemphigoid[112-114]. And there are a randomized, open-label clinical trial compared Niacinamide 500 mg three times daily combined with tetracycline 500 mg four times daily to prednisone 40 to 80 mg per day in 18 bullous pemphigoid patients [115]. The result suggested that Niacinamide with tetracycline therapy may be an effective treatment comparable to prednisolone in selective patients with less adverse effects, such as high blood pressure, gastric ulcer and severe infections which occurred in the prednisone group.

Other than bullous pemphigoid, there is a review of 13 cases in pemphigus vulgaris and linear IgA bullous dermatosis found a successful treatment with oral Niacinamide and tetracycline[116]

2.2.3.4 Niacinamide in atopic dermatitis

Atopic dermatitis (AD) is a chronically relapsing disorder with multiple pathogenesis factors. Patients with AD usually have dry skin and decreasing of ceramide level [117]in stratum corneum. It is essential to have a strong stratum corneum layer because it provides most of the skin's barrier function. AD skin also associated with enhanced transepidermal water loss.[118] Some studies showed that Niacinamide increase the biosynthesis of ceramide and other stratum corneum lipids[80] and decrease transepidermal water loss.[81] Niacinamide may cannot take place of the standard treatment but it might be a useful adjunctive treatment of atopic dermatitis.

2.2.3.5 Niacinamide in aging skin

Substantial improvements in skin appearance, including decreased fine lines and rhytides, hyper-pigmented spots, skin redness, skin discoloration, and better elasticity were identified by a double-blinded, intraindividual, randomized controlled study that applied 5% Niacinamide cream topically and vehicle in 50 Caucasian women for 12 weeks. A cosmetic containing 4% Niacinamide cream or vehicle control cosmetic was applied to the faces of 30 Japanese women for 8 weeks

[119] in another double-blinded, intraindivudual, randomized controlled trial, which also resulted in considerable enhancement in wrinkles and coarse skin.[120]

For the preservation of the epidermal permeability barrier through the control of stratum corneum lipid synthesis, especially related to aged skin, topical Niacinamide could be a significant factor. [80, 81]

2.2.3.6 Niacinamide in Benign hyperpigmentation

The topical use of Niacinamide may be an effective treatment in reducing cutaneous pigmentation. In vivo study showed that Niacinamide inhibits melanosome transfer from melanocytes to keratinocytes and promote skin lightening. [9] There is a double-blinded, randomized controlled trial with 202 patients found that a topical combination of 2% N-acetyl glucosamine and 4% Niacinamide significantly reduced the appearance of irregular pigmentation and providing an effect beyond SPF 15 sunscreen [121].

2.2.3.7 Niacinamide in photocarcinogenesis

Exposure to UV radiation is a potential contributor to both non-melanoma skin cancers (such as basal cell carcinoma and squamous cell carcinoma) and melanomas [122, 123]. DNA damage [124] and UV-induced immunosuppression [125] are the two major pathways used by UVA (320–400 nm) and UVB (290–320 m) radiation to cause skin cancer. [126] [127]

Glycolytic blockade that hinders the enzymes concerned with energy manufacture, resulting in the reduction of ATP in human keratinocytes, may be caused by exposure to UV radiation.[128] Since DNA repair is a very energy-dependent process, this leads to inadequate DNA repair and an elevated risk of genomic transmutations. In UV-irradiated human keratinocyte cultures, Niacinamide has shown the ability to free glycolysis and refill ATP. [92] PARP-1, a significant DNA repair enzyme, can be controlled by Niacinamide. [93] Niacinamide can also boost DNA repair, as found by research employing cultured human keratinocytes and *ex vivo* human skin. [129] Niacinamide can stop the immune-suppressive influences of UV radiation when provided topically at 5% concentration or orally at doses of 500 mg or 1500 mg daily, as found in various animal as well as human studies. [130, 131]or oral route at daily doses of 500 mg or 1500 mg.[132, 133]. Likewise, topical Niacinamide can minimize the immune suppressive consequences of both UVB (300 nm) and long-

wave UVA (385 nm). [134]

Sustained exposure to ultraviolet (UV) radiation can result in the development of Actinic keratoses in the form of cutaneous neoplasms. [1] It is believed that around 0.6% and 3% of AK develops into squamous cell carcinoma after 1 year and 4 years, respectively. [135] There were two studies involving actinic keratosis and Niacinamide, both oral and topical. The first was a phase 2 double-blinded, randomized trial using fit patients who were given oral Niacinamide 500 mg or placebo two times each day for 4 months, which identified a 35% decrease in total AK for the Niacinamide sample when compared to placebo (P = 0.0006). [136] The second was a double-blinded, randomized trial using AK patients who got 1% topical Niacinamide or vehicle two times a day for 6 months, which found that the Niacinamide group had a 22% reduction in AK (P = 0.04) after 3 months. The placebo group only showed a 10% reduction in AK (P = 0.3), which could not be sustained after 6 months. Why the reduction was not sustained remains unclear. [104]

NMSC mainly comprises basal cell carcinomas and squamous cell carcinomas. Significantly decreased occurrences of skin cancer from 75 to 43% (P = 0.016) were found in research on animals using topical Niacinamide in UV-irradiated mice.[130] A dose-dependent reaction of 0.1, 0.5 or 1.0% niacin in dietary supplementation moderates occurrences of skin cancer from 68 to 60%, 48% and 28%, respectively, as found by another murine study.[132]

2.2.3.8 Niacinamide and psoriasis

In vivo study found that Niacinamide established more rapid keratinocyte differentiation. [137] And there is a study used topical treatment with 6-aminonicotinamide to treat psoriasis vulgaris. A 6-aminonicotinamide is the most important antagonist of Niacinamide. It inhibits the stimulation of keratinocyte proliferation from Niacinamide effect in the psoriasis vulgaris patients. [138]

2.2.3.9 Niacinamide and other diseases

Systemic Niacinamide has been used for the treatment of discoid lupus erythematosus in dogs found 70% had excellent or good response to treatment.[139]

Systemic Niacinamide is angiogenic and has been shown to accelerate wound healing and increase rate of viable skin flap in animal studies[140].

Niacinamide enhances the effect of methotrexate (MTX) on murine models of arthritis, and also decrease the hepatotoxicity of MTX. Combination of Niacinamide and methotrexate may be effective in treating psoriatic arthritis.[141]

Niacinamide increases tissue sensitivity to radiotherapy and is useful in cancer therapy[142].

2.3 Review of ANTERA 3D camera

Skin is the biggest organ in human. In the past, dermatologists observed and diagnosed skin diseases with naked eyes but there were limitations. As the technology now has been developed, the dermatologists gradually use medical imaging to help with the clinical diagnose and evaluate treatment response. The famous one is VISIA® complexion analysis system by Canfield Scientific Inc. from United states of America. It uses standard incandescent light, ultraviolet and cross-polarized light to generate a series of high-resolution images. [143]

Recently, there is a new device called 'ANTERA3D®' by Miravex Limited from Ireland. It is a camera that produce images by illuminating the skin with light emitting diodes (LEDs) of seven different wavelengths from different directions (more wavelengths compared with VISIA® which has only three). There was a study found that these two instruments have acceptable correlation in measuring skin color. But ANTERA3D® is more sensitive in assessment of rhytides.[143]

ANTERA3D® can measure and evaluate many skin features including wrinkles, texture, volumes, skin color, redness and pigmentation. It can give the skin's surface in real 3D image. Additionally, it can compare before and after treatment because the software will automatically sync all images with the same attribute to compare with the baseline image that is chosen. It also provides quantitative evidence of treatments' results as shown in figure .[144]

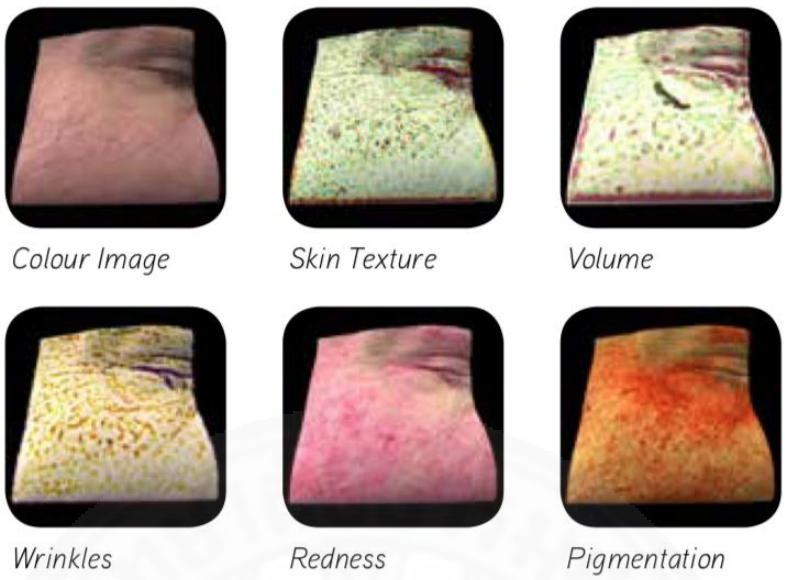


Figure 2.5 Skin features images by ANTERA3D® from limited, m. ANTERA3D. [cited 2018 25June]; Available from: http://miravex.com/.

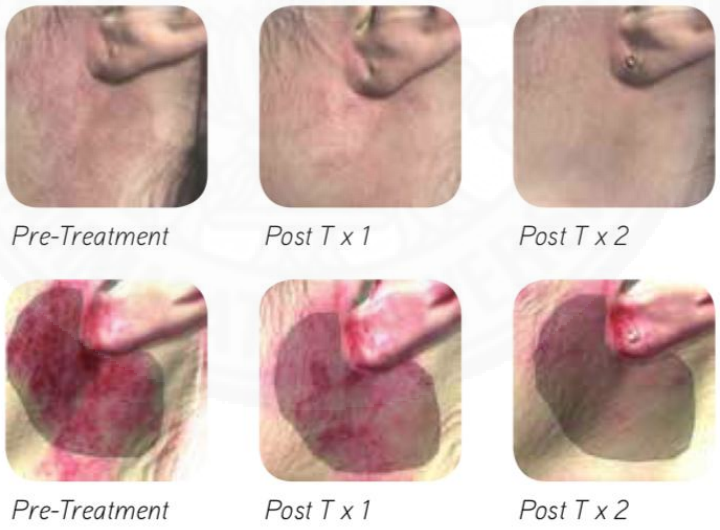


Figure 2.6 Comparison pre and post treatment images by ANTERA3D® from limited, m. ANTERA3D. [cited 2018 25June]; Available from: http://miravex.com/.

2.4 Review of Sebumeter

Sebum hyperproliferation is one of the basic pathogenesis of acne. Human sebum was excreted by sebaceous gland to skin surface. It contains squalene, cholesterol, cholesterol ester, wax esters and triglycerides [1]as shown in figure 2.4 previously. Sebum excretion are regulated by androgens.[1] There are many other factors that affect sebum excretion including diets rich in carbohydrates with a high glycemic index can increase insulin-like growth factor 1 that can stimulate sebaceous gland hypergenesis. Sebum excretion can also vary by age. The highest excretion rate is between 15 – 35 years old and continuously decline when older. Men has higher sebum level than women at any age.[145] Sebum secretion is a circadian rhythm with higher level at noon and lower level in the evening.[146] An increase in 1 °c can produce more sebum excretion rate around 10% due to alteration in sebum viscosity.[145]

In general, there are 2 parameters used for sebum quantification which are casual level and sebum excretion rate. Casual level is a static parameter. It expresses the amount of skin surface lipids. The units are µg/cm². Sebum excretion rate is a dynamic parameter that expresses amount of sebum during a period after delipidization. The units are µg/cm²/min[146]

There are 2 main non-invasive methods have been used based on absorbent paper pads, photometric assessment (e.g. Sebumeter® SM180; CK electronic), bentonite clay and lipid-sensitive tapes (e.g. Sebutape®, CuDerm Corp.) [145]

Sebumeter® is a commercial instrument that investigate sebum casual level by measure transparency of a rough surface of plastic film after painted with lipids. The device contains a cartridge with plastic film that new pieces need to be changed in every measurement. One cartridge contains around 300 times of measurement. The transparency of the plastic film is measured with a photocell after emitted light passes through the plastic strip 2 times. [146]

To start using Sebumeter®, first is correcting calibration. The initial transparency will be displayed “00”. Next, press measuring head against the skin surface for 30 seconds. The display will show count back to zero and give signal sound. The scale is from 0 to 500 and can be transformed to µg/cm². The data will be shown

in bar graph [146]

The advantages of sebumeter are accuracy, reproducibility and easy handling. But it is quite expensive. [146]

Figure 2.7 Sebumeter®[147] from GmbH, C.K.e. Sebumeter® SM 815. 1986 [cited 2018; Available from: https://www.courage-khazaka.de/en/16-wissenschaftliche-produkte/alle-produkte/151-sebumeter-e.

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Primary objective

To evaluate clinical efficacy on non-inflammatory and inflammatory acne lesions of 5%Niacinamide in mild to moderate acne vulgaris treatment

3.2 Secondary objective

3.2.1 To evaluate clinical efficacy in post inflammatory hyperpigmentation of 5%Niacinamide cream compare with cream base for treatment of mild to moderate acne vulgaris

3.2.2 To evaluate clinical efficacy in erythema of 5%Niacinamide cream compare with cream base for treatment of mild to moderate acne vulgaris

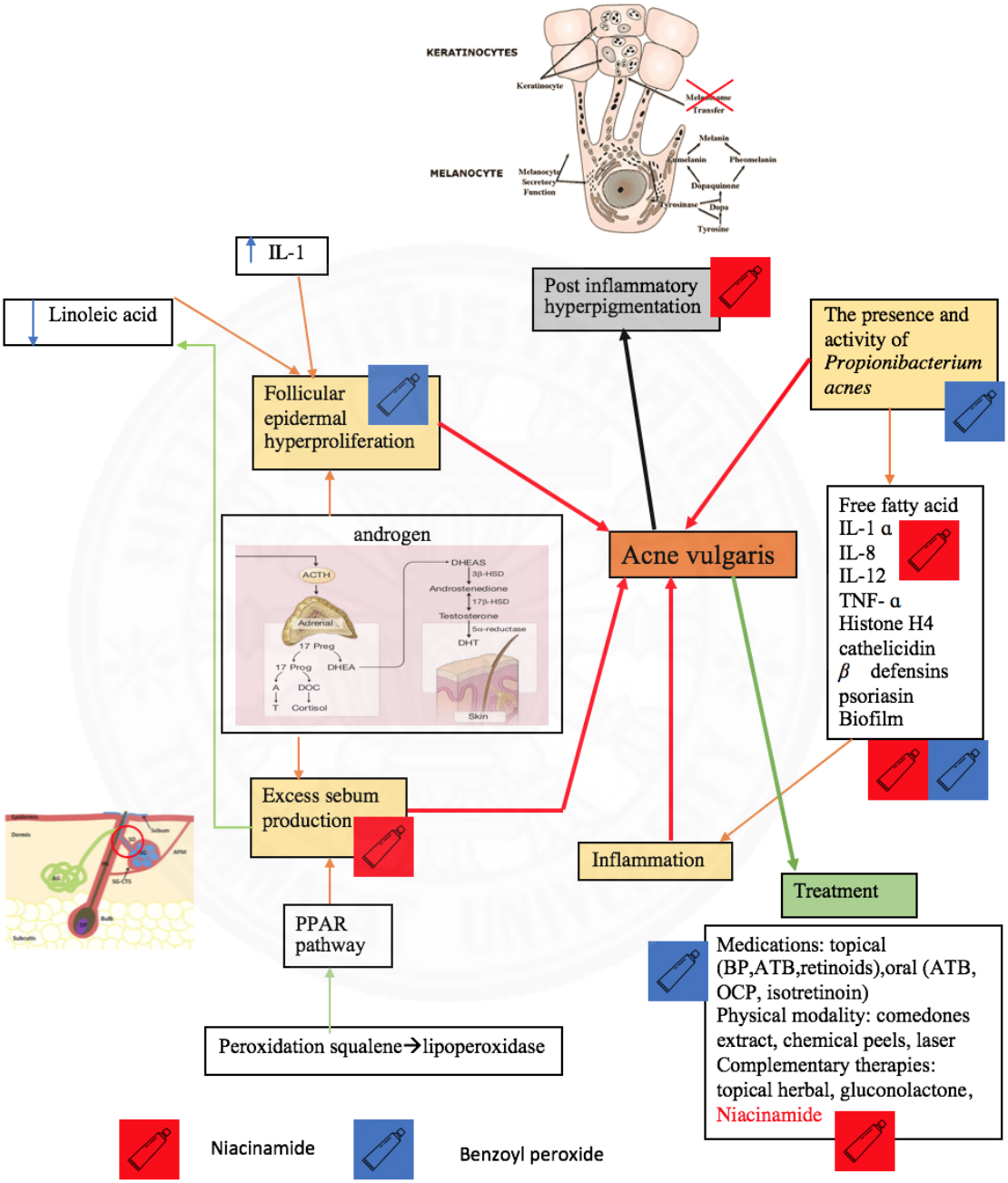
3.2.3 To evaluate clinical efficacy in reduction of facial sebum production of 5%Niacinamide cream compare with cream base for treatment of mild to moderate acne vulgaris

3.2.4 To evaluate side effects of 5%Niacinamide cream compare with cream base in treatment of mild to moderate acne vulgaris

3.3 Hypothesis

5%Niacinamide cream together with 2.5% benzoyl peroxide would improve acne lesions together with improve post inflammatory hyperpigmentation, erythema and reduce facial sebum production better than 2.5% benzoyl peroxide alone

CONCEPTUAL FRAMEWORK



3.4 Study sample

3.4.1 Target population

This study enrolled 21 female and male participants (N=21) age 18-40 years old with mild to moderate acne vulgaris according to grading by The Leeds Revised Acne Grading System[148] as describe in table 9. Study protocol will be summited for approved to Human Ethics committee Thammasat University (Faculty of Medicine) and conducted according to the current versions of the Declaration of Helsinki. All patients will be provided written inform consent.

3.4.2 Sample size

From literature review found that the Niacinamide study group has mean of number of papules (μ_1)24.45±5.39 at week 8, placebo treatment group is expected to have mean of number of papules (μ_2) less than Niacinamide at least 20% [55]

$$n = \left[\frac{(Z_\beta + Z_{\frac{\alpha}{2}})\sigma}{\mu_1 - \mu_2}\right]^2 = \left[\frac{(0.842+1.96)5.39}{23.53-19.56}\right]^2 = 17$$

Figure 3.1 Sample size calculation

Table 3.1 Sample size

μ_1	μ_2	Diff	Sample size	Sample size + **loss 10%**	Sample size + **loss 20%**
23.53	23.23	5%	2536	2790	3043
23.53	22.01	10%	101	111	121
23.53	20.78	15%	33	36	40
23.53	**19.56**	**20%**	**17**	**19**	**20**
23.53	18.34	25%	11	12	13
23.53	17.12	30%	8	9	10

$\beta = 0.2$

power = 0.8

$\alpha = 0.05$

sample size (n) = 17

drop out rate = 20%

At least 20 subjects are included in this study (N=20)

Estimated sample size for comparison of means with Two dependent sample

Formula from: Julious SA. sample sizes for clinical trials with normal data. statistics in medicine. 2004;23(12):1921-1986

3.4.3 Inclusion criteria

3.4.3.1 Healthy Thai females and males age of 18-40 years old

3.4.3.2 willing to and signed inform consent

3.4.3.3 Volunteers who are diagnosed mild to moderate acne vulgaris by using The Leeds revised acne grading system[149] by a physician

3.4.4 Exclusion criteria

3.4.4.1 Receive oral ATB, corticosteroids, oral contraceptive pills, finasteride 1 month prior to study

3.4.4.2 Use topical acne medication 2 weeks prior to study

3.4.4.3 Receive oral retinoid 1 year prior to study

3.4.4.4 Receive dermabrasion, laser resurfacing 2 month prior to study

3.4.4.5 Underlying diseases: endocrine disease, liver disease, active gastrointestinal ulcers or a history of gastrointestinal ulcers, or gout

3.4.4.6 Intramuscular injection of contraceptive, estrogen, steroid within 3 months prior to the study

3.4.4.7 Use medical soap, anti-acne cream and whitening cream within 7 days (allow regular soap and moisturizer)

3.4.4.8 Pregnancy or breastfeeding

3.4.4.9 Heavy smoking (>20 pack-year) and heavy alcohol drinking (5 or more alcoholic drinks for males or 4 or more alcoholic drinks for females on the same occasion for 5 or more days in the past month)

3.4.4.10 Had major surgery within 3 months prior to the study

3.4.4.11 History allergic to topical benzoyl peroxide or Niacinamide

3.4.5 Discontinuation criteria

3.4.5.1 Dramatically change in acne symptoms such as severe acne, acne fulminans that require other treatment assessed by dermatologist

3.4.5.2 Subjects who are unwilling to comply with the study requirements

3.5 Research design

Interventional therapeutic trial, a prospective, double-blinded, split-face, randomized control trial will be conduct between November to February 2018.

3.6 Material and methods

3.6.1 Study procedures

3.6.1.1 Apply 2.5%benzoyl peroxide water-base gel 2 FTU (1g) on the entire face 10 minutes before facial washing twice daily in the morning and before bedtime

3.6.1.2 After washing 2.5%benzoyl peroxide water-base gel apply 5%Niacinamide gel 1 FTU (0.5g) on one half-face

3.6.1.3 Wash both hands with soap and dry with towel

3.6.1.4 Apply placebo gel 1 FTU(0.5g) on another half

3.6.1.5 Do this procedure twice daily in the morning and before bedtime

Half face is separated by a straight imaginary line which starts from mid glabella to nose tip and the most prominent point of chin.

3.6.1.6 Keep the medical drugs in a cool dry place where the temperature stays below 25^0C. Keep it where children cannot reach it.

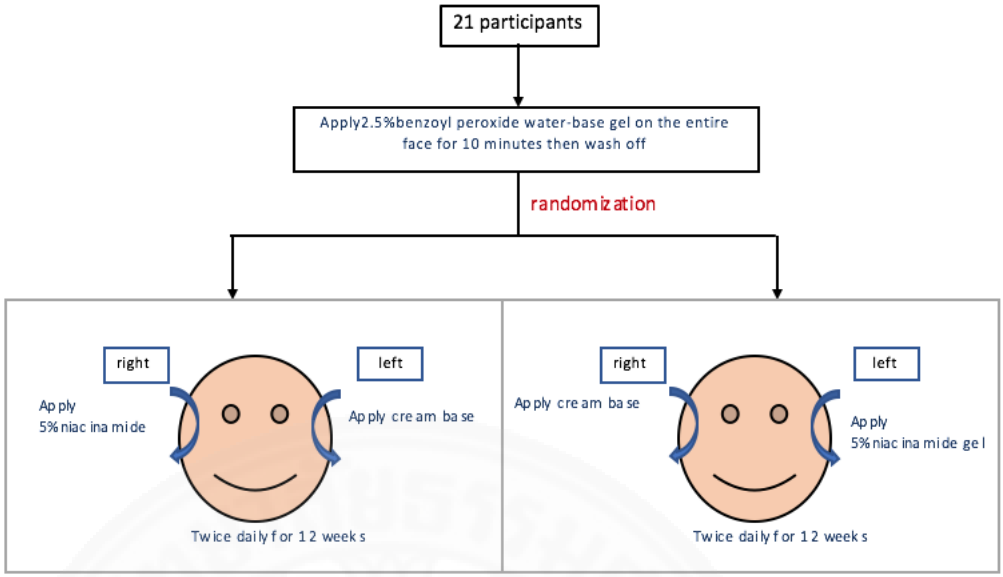


Figure 3.2 Research methodology

3.6.2 Randomization and masking

Neither the investigator nor the participants know which drugs will be administered. A randomization code list generated by the statistician for packaging and labelling of the study medication and also produce randomized code envelopes. The participants will receive all study medications from research assistant at Thai tobacco monopoly hospital

3.6.3 Study place

Study will be conducted at Thai tobacco monopoly hospital.

3.6.4 Preparation of the research subjects

3.6.4.1 Subjects will be selected to enroll in the study according to the selection criteria

3.6.4.2 Details in the information sheet will be inform to all subjects

3.6.4.3 The subjects will sign an inform consent form for participation in the study

3.6.4.4 The information of subjects will be recorded.

3.6.5 Outcome measurement

Each patient will have 7 followed up visit for clinical evaluation at week 0,2,4,6,8,10,12

3.6.5.1 Evaluation of efficacy

(1) Total lesion counts, non-inflammatory and inflammatory acne from clinical presentation at outpatient department at initial and 2, 4, 6, 8,10, 12 weeks after treatment recorded by physician

(2) Post acne erythema score by ANTERA® 3D on lesion site (use lesion site as a center of photo) and use same lesion at initial and 2, 4, 6, 8,10, 12 weeks after treatment

(3) Post inflammatory hyperpigmentation score by ANTERA ® 3D on lesion site (use lesion site as a center of photo) and use same lesion at initial and 2, 4, 6, 8,10, 12 weeks after treatment

(4) Sebum casual level by a Sebumeter ® SM 815 (Courage & Khazaka, Ko¨ln or Cologne, Germany) on two different sites of the face: right and left cheeks (the most prominent area of both zygomas) at initial and 2, 4, 6, 8,10, 12 weeks after treatment

*the participants will be asked to clean their face with facial cleanser and wait for 1 hour before sebum casual level measurement to determine sebum on the skin surface

Figure 3.3 Sebumeter® from GmbH, C.K.e. Sebumeter® SM 815. 1986 [cited 2018; Available from: https://www.courage-khazaka.de/en/16-wissenschaftliche-produkte/alle-produkte/151-sebumeter-e.

Figure 3.4 Antera® 3D camera from [144] from limited, m. ANTERA3D. [cited 2018 25June]; Available from: http://miravex.com/.

3.6.5.2 Evaluation of satisfaction

(1) Physician improvement scale: the grading, based on clinical presentation at outpatient department, will be recorded by single physician at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks and 12 weeks after treatment according to 0-4 point scale (table3.2)

Table 3.2 Physician improvement scale

0	No change (0%)
1	Slight improvement (0-25%)
2	Moderate improvement (26-50%)
3	Significant improvement (51-75%)
4	Excellent improvement (76-100%)

(2) Patient satisfaction index: patient will be asked to grade the satisfaction score using 0 - 4 point scale of each facial side at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks and 12 weeks after treatment (table 3.3)

Table 3.3 Patient satisfaction index

0	No change (0%)
1	Slight improvement (0-25%)
2	Moderate improvement (26-50%)
3	Significant improvement (51-75%)
4	Excellent improvement (76-100%)

3.6.5.3 Evaluation of safety

Adverse effects will be evaluated by patient evaluation form asking if they have itching, burning, crusting, greasy, dermatitis or not

3.6.5.4 Evaluation of accuracy in application of Niacinamide and placebo cream by participants

The participants were given 1 box of Niacinamide cream and 1 box of placebo cream every visit (2 weeks interval). Each box contains the same amount (15g) of cream. The participants were asked to finish all cream in the boxes.

3.6.6 Data analysis

Results expressed as mean +/- standard deviation or median and range were used to describe patients' characteristics. Categorical variables were compared using Chi-squared test or Fisher's exact test. Continuous variables were compared using t-test or Mann-Whitney U-test. A mixed effect linear regression model was applied to assess and compare Number of papules between two intervention groups. All analyses were performed using STATA version 13.1. P-value of less than 0.05 was considered statistical significance.

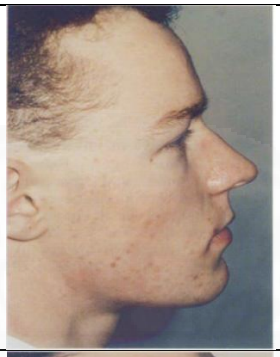
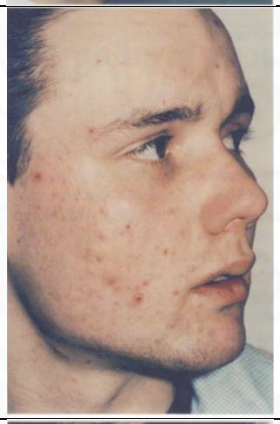
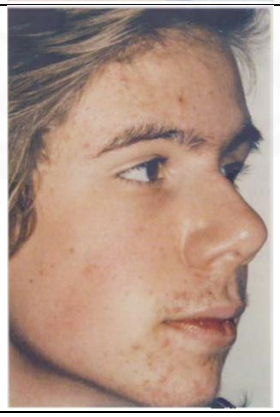
3.6.7 Follow up plan

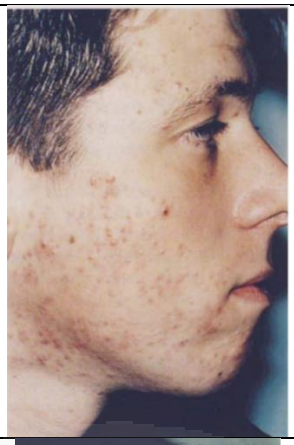
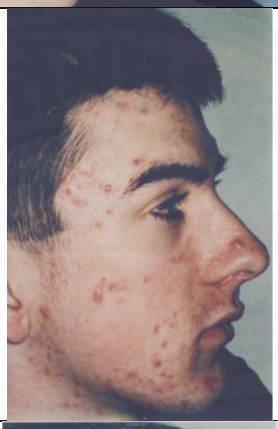
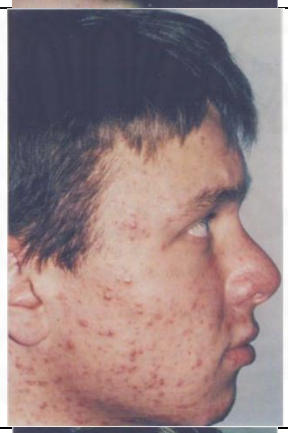
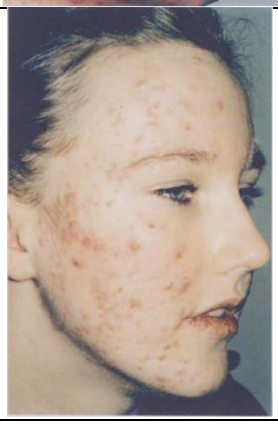
Table 3.4 Follow up plan

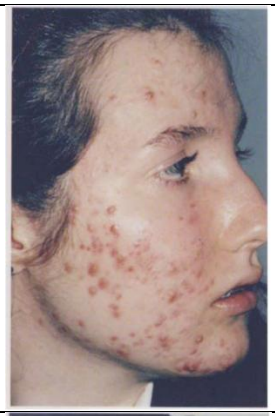
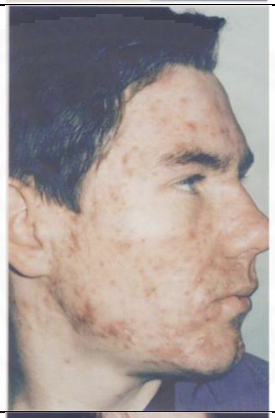
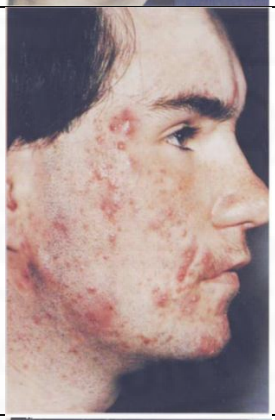
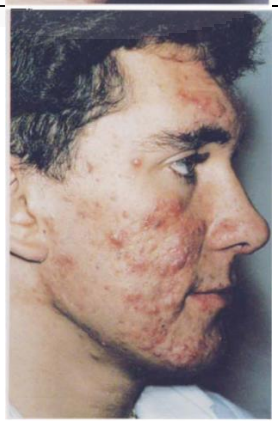
assessment	baseline	2nd week	4th week	6th week	8th week	10th week	12th week
Photograph	/	/	/	/	/	/	/
Acne count	/	/	/	/	/	/	/
Antera 3D	/	/	/	/	/	/	/
Sebumeter	/	/	/	/	/	/	/
Patient evaluation form		/	/	/	/	/	/
Physician improvement scale		/	/	/	/	/	/
Side effects		/	/	/	/	/	/

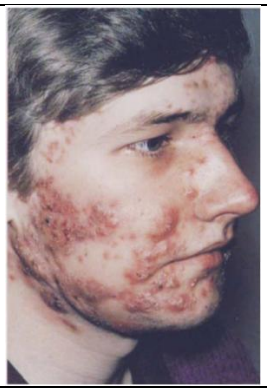
*at 1st week patients will receive a call from a blinded dermatologist for evaluation irritation and problems.

Table 3.5 [149] The Leeds Revised Acne Grading System from SCO'Brien, J.L.a.W.C., The Leeds revised acne grading system. Journal of Dermatoloqical Treatment, 1998(9): p. 215-220.

Acne Severity		picture	Clinical features
Mild	Grade 1		mostly are comedones or papule and pustule less than 10
	Grade 2		
	Grade 3		

	Grade 4		
Moderate	Grade 5		papules and pustules more than 10 and/or nodules less than 5
	Grade 6		
	Grade 7		

	Grade 8		
Severe	Grade 9		- many papules, pustules, nodules or cysts - recurrent papules, pustules nodules or cyst - sinus tract
	Grade 10		
	Grade 11		

	Grade 12		

3.6.7 Time frame

Table 3.6 Time frame

	2017		**2018**											**2019**					
	NOV	**DEC**	**JAN**	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**	**AUG**	**SEP**	**OCT**	**NOV**	**DEC**	**JAN**	**FEB**	**MAR**	**APR**	**MAY**
Review literature																			
Drafting proposal																			
Ethic approval																			
Patients collection																			
Data analysis																			
Manuscript preparation																			

CHAPTER 4
RESULTS

4.1 Demographic data

21 patients (16 females and 5 males) with facial acne vulgaris (7 patients with moderate facial acne vulgaris and 14 patients with mild facial acne vulgaris using the Leeds revised grading system) were included in this study. The age of the patients was in a range from 18 to 36. There were 4 missing patients from this study during 12 weeks. The details of the demographic data were shown in Table 4.1

Table 4.1 Demographic data of each participant

Subject No.	Age	Gender	Severity by the Leeds revised acne grading system	Niacinamide side	Cream base side
1	29	Male	Mild	Left	Right
2	38	Female	Mild	Right	Left
3	35	Female	Mild	Left	Right
4	19	Female	Mild	Right	Left
5	30	Female	Moderate	Left	Right
6	28	Female	Mild	Left	Right
7	36	Male	Moderate	Right	Left
8	23	Female	Moderate	Right	Left
9	34	Female	Mild	Left	Right
10	24	Female	Mild	Right	Left

11	19	Male	Mild	Right	Left
12	30	Female	Moderate	Left	Right
13	18	Male	Moderate	Left	Right
14	18	Female	Mild	Right	Left
15	27	Female	Mild	Left	Right
16	23	Female	Moderate	Left	Right
17	21	Female	Moderate	Right	Left
18	20	Female	Mild	Left	Right
19	21	Female	Mild	Right	Left
20	19	Female	Mild	Right	Left
21	31	Male	Mild	Right	Left

Table 4.2 Statistical analysis of demographic data

Variables	**Statistics**
Age (years)	
Mean+-SD	25.86±6.49
Min-Max	18-38
Gender, n (%)	
Female	16(76%)
Male	5(24%)
Acne severity, n (%)	
Mild	17(67%)
Moderate	7(33%)

According to **Table 4.2** demonstrated that most of subjects were female (76%) more than male (24%). The mean age was 26 years old. All subjects were evaluated acne severity by using the Leeds revised grading system found that 67% were mild severity and 33% were moderate severity.

4.2 Clinical evaluation

All enrolled patients were evaluated for non-inflammatory and inflammatory acne lesion counts, sebum casual level by Sebumeter ®. Patients were also evaluated for post acne erythema and post inflammatory hyperpigmentation by Antera 3D® in every visit. Clinical visit was scheduled at baseline, week 2, week 4, week 6, week 8, week 10 and week 12.

Table 4.3 Non-inflammatory lesion counts

Subject No.	**Right**							**Left**						
	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	10	15	30	20	15	10	9	15	14	22	15	12	8	12
2	10	-	-	-	-	-	-	7	-	-	-	-	-	-
3	22	20	14	23	21	12	8	18	17	10	25	23	16	10
4	30	16	15	12	7	10	10	21	7	9	11	13	8	12
5	24	33	17	22	21	20	20	27	31	15	19	15	24	18
6	41	23	20	25	21	28	12	43	28	22	29	13	23	10
7	45	43	31	33	32	34	28	29	25	22	25	30	31	30
8	19	18	17	-	-	-	-	16	17	22	-	-	-	-
9	34	23	21	19	18	13	12	44	25	15	21	16	9	9
10	38	35	32	21	20	24	8	23	27	23	18	16	19	10
11	21	18	11	32	-	-	-	30	25	12	25	-	-	-
12	32	-	-	-	-	-	-	33	-	-	-	-	-	-
13	36	26	29	28	26	25	23	39	23	26	19	23	22	19
14	43	39	28	31	22	28	22	40	38	27	35	25	20	20
15	12	6	6	4	10	12	13	10	7	8	6	12	11	9
16	25	31	32	31	19	18	19	30	25	35	20	12	20	16
17	42	34	30	44	36	32	30	46	46	32	39	21	35	36

18	19	6	11	12	9	12	10	21	12	13	13	11	12	8
19	32	22	17	20	11	8	10	19	9	10	11	8	11	16
20	10	12	8	8	9	11	6	9	10	5	5	9	10	10
21	23	14	14	16	13	8	6	21	23	21	13	15	5	4

Table 4.4 Non-inflammatory lesion counts at baseline, week 2, week 4, week 6, week 8, week 10, week 12 compared between Niacinamide group and cream base group

Time	Treatment Group	N	mean	SE	Co ef.	Lower 95%	Upper 95%	P value
Baseline	Niacinamide Cream base	21	28.24 24.57	2.63 2.38	3.67	-1.94	9.27	0.2
Week2	Niacinamide Cream base	19	22.79 21.58	2.3 2.55	1.09	-4.67	6.84	0.71
Week4	Niacinamide Cream base	19	19.11 19.11	2.04 1.99	-0.12	-5.88	5.63	0.97
Week6	Niacinamide Cream base	18	21.33 20.33	2.27 2.3	0.78	-5.04	6.6	0.79
Week8	Niacinamide Cream base	17	16.88 17.47	1.96 1.56	-1.02	-6.92	4.87	0.73
Week10	Niacinamide Cream base	17	17.65 17	2.14 2.08	0.21	-5.68	6.1	0.94
Week12	Niacinamide Cream base	17	13.59 15.53	1.79 2.01	-2.38	-8.27	3.52	0.43

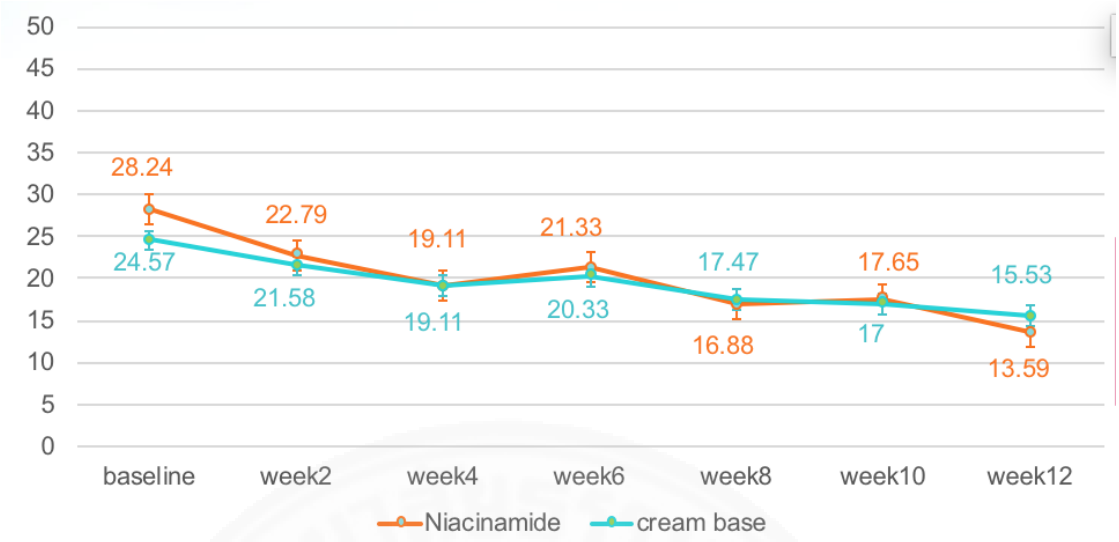


Figure 4.1 Graph of non-inflammatory lesion counts

Table 4.3 demonstrates non-inflammatory lesion counts of all subjects in each visit. The number of non-inflammatory lesion were counted by physician at Thai tobacco monopoly hospital at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. The statistical analysis was evaluated to compare between Niacinamide group and cream base group at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. Mean of non-inflammatory lesion counts was not statistical difference at the beginning and tended to decrease in both groups as shown in **Table 4.4** and **Figure 4.1.**

Table 4.5 Non-inflammatory lesion counts change from baseline in each visit

Time	Niacinamide	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	-5.94	-9.21	-2.67	0.000
Wk4	-9.62	-12.89	-6.36	0.000
Wk6	-7.67	-10.991	4.34	0.001
Wk8	-12.27	-15.65	-8.88	0.000
Wk10	-11.5	-14.89	-8.12	0.000
Wk12	-15.56	-18.95	-12.17	0.000
Time	Cream base	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	-3.36	-6.61	-0.11	0.08
Wk4	-5.83	-9.08	-2.58	0.01
Wk6	-4.78	-8.08	-1.47	0.002
Wk8	-7.57	-10.94	-4.2	0.000
Wk10	-8.04	-11.41	-4.67	0.000
Wk12	-9.51	-12.88	-6.14	0.001

Table 4.6 Non-inflammatory lesions change from baseline (%) to week 12

Treatment	Mean	P value
Niacinamide	-51	0.004
Cream base	-34	

Table 4.5 and **Table 4.6** was shown that non-inflammatory lesion counts were decreased very significantly since week 2 (p=0.000) in Niacinamide group and continue to decrease statistically significant in every visit (p=0.000) compare to Cream base group which started to decrease significantly at week4 (p=0.01). Non-inflammatory lesions count from baseline at week 12 decreased more in Niacinamide group, which was 51%, than Cream base group, which was 34%. And it was statistically significant difference (P=0.004)

Table 4.7 Inflammatory lesion counts

Subject No.	**Right**							**Left**						
	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	5	6	1	0	0	0	1	7	2	1	0	0	0	2
2	6	-	-	-	-	-	-	5	-	-	-	-	-	-
3	2	1	4	0	1	2	2	1	0	3	1	0	0	1
4	0	3	0	1	0	4	2	1	2	0	0	0	4	1
5	5	2	4	2	6	3	3	6	5	3	3	2	3	3
6	15	0	2	1	1	3	0	12	0	2	1	3	1	0
7	12	12	11	10	2	5	2	8	4	9	4	1	0	2
8	7	4	2	-	-	-	-	6	3	1	-	-	-	-
9	0	0	2	1	0	1	2	7	3	0	1	1	1	1
10	2	3	0	1	0	1	0	1	1	1	2	0	0	2
11	1	1	1	3	-	-	-	2	2	1	2	-	-	-
12	1	-	-	-	-	-	-	4	-	-	-	-	-	-
13	4	3	3	3	3	2	3	5	3	2	0	2	2	2
14	6	3	3	1	1	3	1	4	2	4	0	0	1	1
15	0	1	0	0	1	3	1	0	0	0	0	0	0	0
16	4	4	2	3	6	6	4	2	3	3	3	1	4	3
17	7	5	4	6	4	8	1	5	2	3	8	6	11	3
18	4	2	0	1	2	2	2	1	1	0	1	3	3	1

19	4	3	2	1	2	2	1	3	0	2	1	1	3	2
20	2	1	2	2	0	2	1	3	1	3	1	3	1	0
21	3	1	1	0	0	1	0	3	1	0	0	0	0	0

Table 4.7 demonstrates inflammatory lesion counts of all subjects in each visit. The number of inflammatory lesion were counted by physician at Thai tobacco monopoly hospital at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. The statistical analysis was evaluated to compare between Niacinamide group and cream base group at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. Mean of inflammatory lesion counts was not statistical difference at the beginning and tended to decrease in both groups as shown in **Table 4.8** and **Figure 4.2.**

From **Table 4.9** and **Table 4.10,** it is shown that Niacinamide group had a decrease in inflammatory lesion counts significantly since first follow up visit ($p=0.002$) and after 4 weeks it was very significant ($p<0.001$) in all later visits compare to Cream base group which also decreased significantly since week 2 ($p=0.002$) but very significant decrease ($p<0.001$) occurred only at week 6. The change in inflammatory lesion counts at week 12 was decreased 57% and 44% from baseline in Niacinamide group and cream base group respectively. But the change between 2 groups were not statistically difference ($P=0.63$)

Table 4.8 Inflammatory lesion counts at baseline, week 2, week 4, week 6, week 8, week 10, week 12 compared between Niacinamide group and cream base group

Time	Treatment Group	N	mean	SE	Co ef.	Lower 95%	Upper 95%	P value
Baseline	Niacinamide Cream base	21	4.52 3.86	0.76 0.71	0.67	-0.71	2.04	0.24
Week2	Niacinamide Cream base	19	2.79 1.95	0.62 0.35	0.89	-0.55	2.33	0.23
Week4	Niacinamide Cream base	19	2.11 2.21	0.57 0.49	-0.57	-1.49	1.38	0.6
Week6	Niacinamide Cream base	18	1.94 1.61	0.59 0.47	0.4	-1.07	1.87	0.3
Week8	Niacinamide Cream base	17	1.24 1.82	0.32 0.54	-0.54	-2.05	0.96	0.45
Week10	Niacinamide Cream base	17	2.35 2.48	0.51 0.66	-0.74	-1.57	1.43	0.72
Week12	Niacinamide Cream base	17	1.24 1.76	0.24 0.28	-0.43	-1.93	1.07	0.07

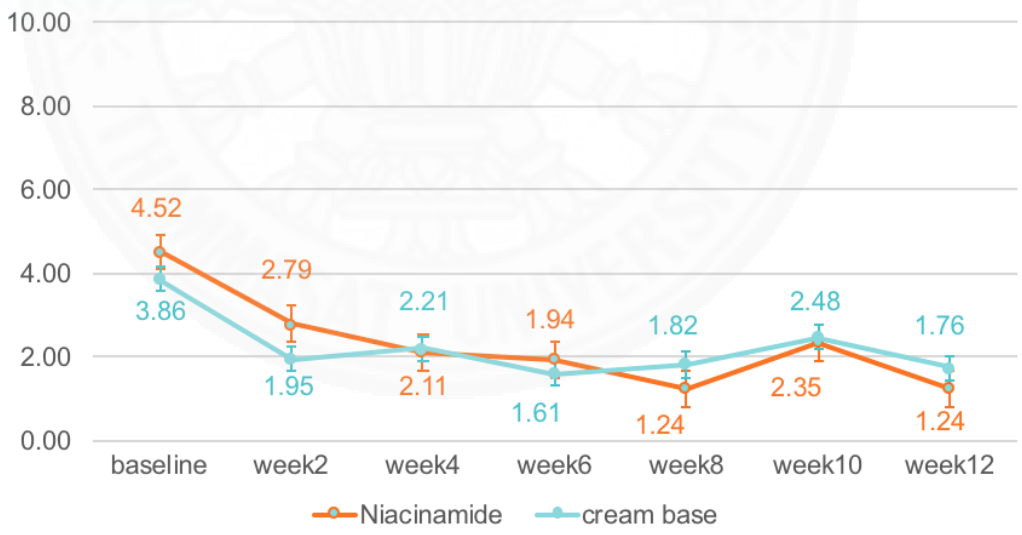


Figure 4.2 Graph of inflammatory lesion counts

Table 4.9 Inflammatory lesion counts change from baseline in each visit

Time	Niacinamide	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	-1.71	-2.8	-0.62	0.002
Wk4	-2.4	-3.49	-1.31	0.000
Wk6	-2.51	-3.62	-1.40	0.000
Wk8	-3.28	-4.41	-2.15	0.000
Wk10	-2.16	-3.29	-1.03	0.000
Wk12	-3.28	-4.41	-2.15	0.000
Time	Cream base	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	-1.93	-3.14	-0.73	0.002
Wk4	-1.67	-2.87	-0.46	0.007
Wk6	-2.25	-3.48	-1.02	0.000
Wk8	-2.06	-3.31	-0.81	0.001
Wk10	-1.41	-2.66	-0.16	0.027
Wk12	-2.18	-3.42	-0.93	0.001

Table 4.10 Inflammatory lesions change from baseline (%) to week 12

Treatment	Median	P value
Niacinamide	-57	0.63
Cream base	-44	

Table 4.11 Sebum casual level

Subject No.	**Right**							**Left**						
	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	89	97	97	60	53	70	86	82	92	62	54	54	73	64
2	15	-	-	-	-	-	-	21	-	-	-	-	-	-
3	16	14	18	22	31	17	10	11	10	15	19	17	13	14
4	39	29	81	78	37	32	29	37	21	62	59	37	45	28
5	34	55	40	32	21	29	20	28	27	39	28	20	21	29
6	20	25	23	49	23	25	18	26	22	20	32	30	16	18
7	29	30	21	18	22	27	23	23	23	25	15	30	18	14
8	54	57	60	-	-	-	-	53	65	61	-	-	-	-
9	60	31	31	27	27	41	36	59	49	20	25	18	29	24
10	23	33	23	15	13	23	22	18	19	20	16	16	19	21
11	22	18	24	21	-	-	-	24	20	37	17	-	-	-
12	15	-	-	-	-	-	-	16	-	-	-	-	-	-
13	62	50	58	64	58	46	35	67	47	42	36	48	25	29
14	45	29	19	21	28	28	25	38	33	24	25	24	26	19
15	12	12	22	14	16	15	11	20	21	21	13	17	11	11
16	95	86	121	62	62	82	89	86	77	99	53	57	83	85
17	18	18	18	16	18	17	13	11	16	24	13	11	24	15

18	32	30	37	34	27	33	30	34	30	33	42	31	31	28
19	29	21	23	22	22	16	15	24	33	29	17	30	30	22
20	28	22	28	21	25	18	16	28	27	22	16	21	20	16
21	50	42	61	47	50	39	35	65	62	61	47	44	41	39

Table 4.11 demonstrates sebum casual level by Sebumeter® of all subjects in each visit. The room temperature was controlled at 23-25°c and the humidity was around 40-60% in dermatology outpatient department at Thai tobacco monopoly hospital measured by sensor RTH 100 at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. The statistical analysis was evaluated to compare between Niacinamide group and cream base group at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. Mean of sebum casual level was not statistical difference at the beginning and tended to decrease in both groups as shown in **Table 4.12** and **Figure 4.3.**

According to **Table 4.13** and **Table 4.14,** it is shown that sebum casual level started to decrease significantly from baseline since week 6 in Niacinamide group compare to Cream base group which decreased significantly only at week 8 and week 12. From **Table 4.12**, mean of sebum casual in Niacinamide group was lower than Cream base group significantly at week 4 (p=0.02) and week 10 (p=0.03). The change in sebum casual level at week 12 was decreased 26 % and 20% from baseline in Niacinamide group and cream base group respectively. But it was not statistically difference (P=0.26)

Table4.12 Sebum casual level at baseline, week 2, week 4, week 6, week 8, week 10, week 12 compared between Niacinamide group and cream base group

Time	Treatment Group	N	mean	SE	Co ef.	Lower 95%	Upper 95%	P value
Baseline	Niacinamide Cream base	21	37.19 37	4.74 5.36	0.19	-12.31	12.69	0.69
Week2	Niacinamide Cream base	19	35.47 37.84	4.84 5.65	-2.59	-15.33	10.14	0.33
Week4	Niacinamide Cream base	19	37.32 42.74	5.53 6.43	-5.65	-18.38	7.09	0.02
Week6	Niacinamide Cream base	18	31.17 32.72	4.11 4.45	-1.79	-14.63	11.04	0.66
Week8	Niacinamide Cream base	17	29.82 31.24	3.47 3.63	-1.71	-14.64	11.23	0.45
Week10	Niacinamide Cream base	17	29.53 34.18	4.8 4.53	-4.94	-17.88	7.99	0.03
Week12	Niacinamide Cream base	17	28.18 29.94	4.63 5.66	-2.06	-15	10.88	0.41

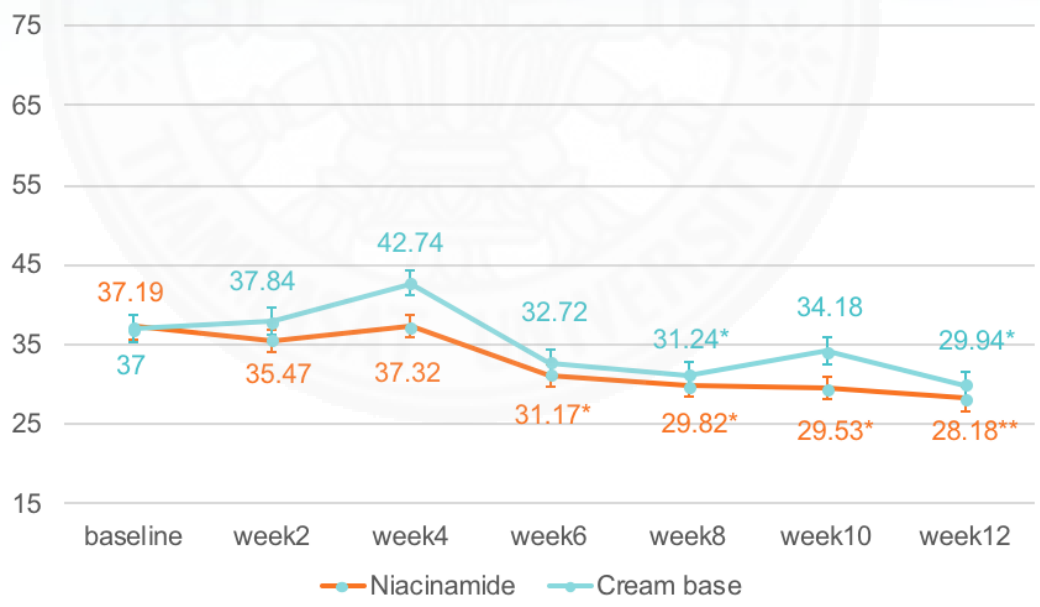


Figure 4.3 Graph of sebum casual level

Table 4.13 Sebum casual level change from baseline in each visit

Time	Niacinamide	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	-3.49	-9.36	2.38	0.24
Wk4	-1.65	-7.51	4.22	0.58
Wk6	-6.8	-12.78	-0.83	0.03
Wk8	-8.9	-14.99	-2.82	0.004
Wk10	-9.2	-15.28	-3.12	0.003
Wk12	-10.55	-16.64	-4.47	0.001
Time	Cream base	Lower 95%	Upper95%	P value
Wk0	0	--	-	-
Wk2	-0.79	-6.64	5.06	0.79
Wk4	4.1	-1.75	9.95	0.17
Wk6	-4.89	-10.84	1.07	0.11
Wk8	-7.09	-13.15	-1.02	0.02
Wk10	-4.15	-10.21	1.92	0.18
Wk12	-8.38	-14.45	-2.32	0.007

Table 4.14 Sebum casual level change from baseline (%) to week 12

Treatment	Mean	P value
Niacinamide	-26	0.26
Cream base	-20	

Table 4.15 Post acne erythema score from ANTERA 3D® camera

Subject No.	Right							Left						
	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	1.652	1.577	1.573	1.654	1.66	1.559	1.688	1.75	1.589	1.718	1.675	1.774	1.717	1.698
2	1.703	-	-	-	-	-	-	1.704	-	-	-	-	-	-
3	1.601	1.524	1.502	1.599	1.61	1.52	1.664	1.526	1.514	1.513	1.389	1.559	1.519	1.601
4	1.552	1.497	1.505	1.446	1.37	1.393	1.481	1.496	1.526	1.567	1.52	1.415	1.532	1.607
5	1.265	1.42	1.396	1.44	1.63	1.548	1.555	1.457	1.645	1.64	1.621	1.697	1.7	1.691
6	1.459	1.531	1.365	1.464	1.436	1.407	1.402	1.48	1.55	1.365	1.464	1.436	1.407	1.402
7	1.859	1.934	1.649	1.774	1.685	1.841	1.69	1.834	1.815	1.591	1.512	1.492	1.621	1.536
8	1.435	1.566	1.571	-	-	-	-	1.708	1.696	1.67	-	-	-	-
9	1.31	1.372	1.317	1.253	1.256	1.349	1.302	1.329	1.397	1.332	1.418	1.304	1.371	1.373
10	1.475	1.5	1.619	1.484	1.602	1.616	1.457	1.588	1.649	1.618	1.595	1.543	1.615	1.456
11	1.706	1.68	1.609	1.837	-	-	-	1.616	1.663	1.741	1.896	-	-	-
12	1.432	-	-	-	-	-	-	1.556	-	-	-	-	-	-
13	1.582	1.435	1.479	1.52	1.482	1.441	1.425	1.539	1.344	1.384	1.347	1.357	1.313	1.31
14	1.574	1.553	1.654	1.562	1.595	1.674	1.719	1.566	1.494	1.611	1.495	1.43	1.571	1.635
15	1.554	1.426	1.433	1.343	1.343	1.36	1.412	1.61	1.404	1.399	1.363	1.528	1.451	1.539
16	1.254	1.306	1.258	1.33	1.417	1.422	1.486	1.253	1.367	1.247	1.377	1.431	1.36	1.369
17	1.438	1.557	1.374	1.502	1.419	1.269	1.237	1.263	1.239	1.14	1.354	1.501	1.386	1.406

18	1.371	1.275	1.244	1.384	1.404	1.455	1.391	1.357	1.313	1.244	1.242	1.423	1.403	1.441
19	1.35	1.353	1.254	1.416	1.369	1.419	1.468	1.571	1.448	1.352	1.356	1.482	1.491	1.559
20	1.29	1.146	1.294	1.427	1.465	1.23	1.269	1.243	1.146	1.214	1.495	1.326	1.255	1.243
21	1.291	1.285	1.508	1.546	1.618	1.607	1.579	1.455	1.519	1.553	1.464	1.552	1.512	1.524

Table 4.15 demonstrates post acne erythema scores by ANTERA 3D® camera of all subjects in each visit. The ANTERA 3D images was taken at both cheeks of all subjects at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. The statistical analysis was evaluated to compare between Niacinamide group and cream base group at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. Mean of post acne erythema score was not statistical difference at the beginning and was slightly increased as shown **Table 4.12** and **Figure 4.3.**

According to **Table 4.17** and **Table 4.18,** it is shown that post acne erythema slightly increased from baseline at the end of week 12 with no statistical difference in both groups. The change in post acne erythema score at week 12 was decreased 0.5% and increased 1.5% from baseline in Niacinamide group and cream base group respectively. But the change between 2 groups were not statistically difference (P=0.98)

Table 4.16 Post acne erythema score at baseline, week 2, week 4, week 6, week 8, week 10, week 12 compared between Niacinamide group and cream base group

Time	Treatment Group	N	mean	SE	Co ef.	Lower 95%	Upper 95%	P value
Baseline	Niacinamide Cream base	21 21	1.501 1.501	0.036 0.037	0.000	-0.917	0.092	0.99
Week2	Niacinamide Cream base	19 19	1.484 1.477	0.04 0.038	0.012	-0.829	0.106	0.81
Week4	Niacinamide Cream base	19 19	1.481 1.454	0.036 0.039	0.031	-0.064	0.125	0.34
Week6	Niacinamide Cream base	18 18	1.494 1.482	0.036 0.035	0.008	-0.087	0.103	0.7
Week8	Niacinamide Cream base	17 17	1.51 1.47	0.032 0.026	0.034	-0.062	0.131	0.11
Week10	Niacinamide Cream base	17 17	1.486 1.473	0.043 0.025	0.007	-0.895	0.104	0.62
Week12	Niacinamide Cream base	17 17	1.494 1.488	0.037 0.03	0.000	-0.097	0.097	0.8

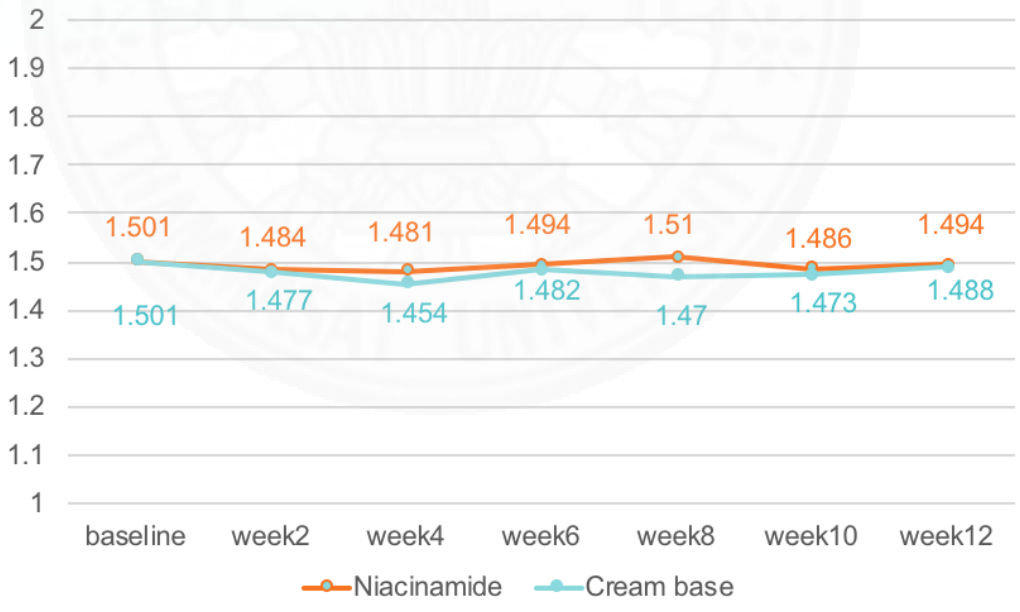


Figure 4.4 Graph of post acne erythema score

Table 4.17 Post acne erythema score change from baseline in each visit

Time	Niacinamide	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	-0.008	-0.061	0.045	0.77
Wk4	-0.012	-0.065	0.041	0.67
Wk6	0.004	-0.499	0.058	0.88
Wk8	0.032	-0.229	0.087	0.25
Wk10	0.008	-0.465	0.063	0.77
Wk12	0.016	-0.39	0.07	0.57
Time	Cream base	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	-0.019	-0.07	0.032	0.46
Wk4	-0.042	-0.094	0.009	0.11
Wk6	-0.004	-0.562	0.048	0.89
Wk8	-0.003	-0.558	0.051	0.93
Wk10	0.001	-0.052	0.055	0.96
Wk12	0.016	-0.037	0.069	0.56

Table 4.18 Post acne erythema score change from baseline (%) to week 12

Treatment	Median	P value
Niacinamide	-0.47	0.98
Cream base	1.46	

Figure 4.5 and Figure 4.6 below are images from ANTERA 3D® camera in Hemoglobin (Hb) index mode to analyze post acne erythema score.

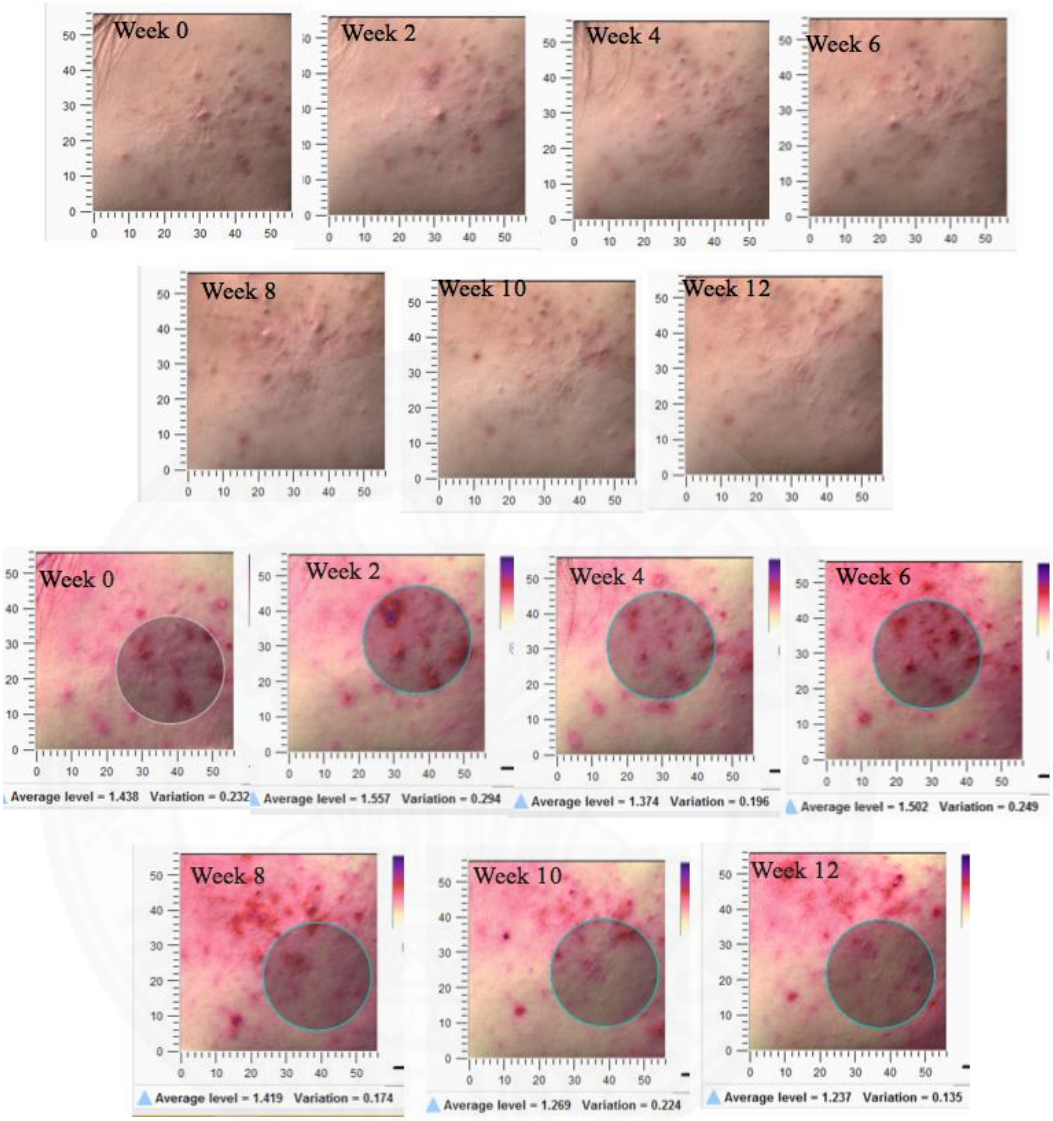


Figure 4.5 post acne erythema images and scores of Niacinamide group by ANTERA 3D® camera of subject No.17

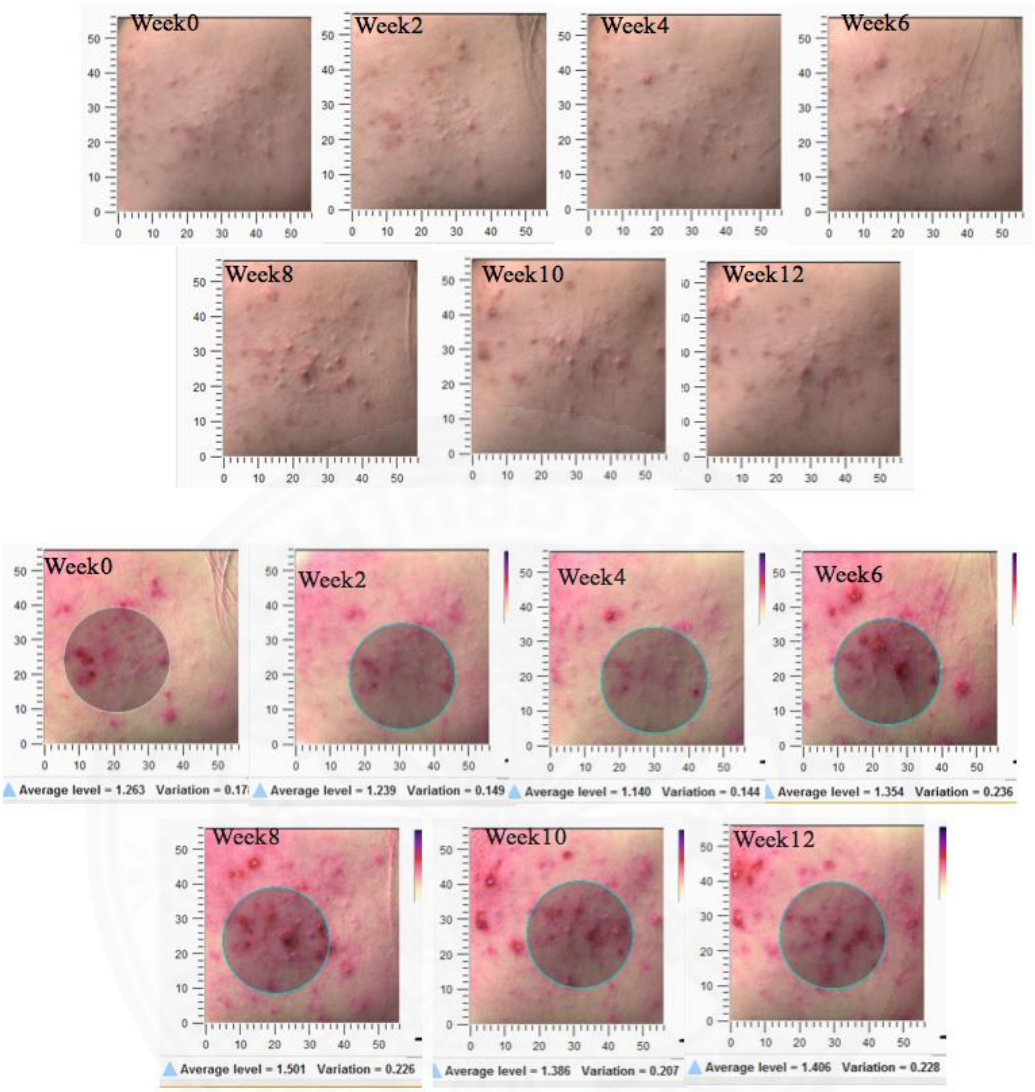


Figure 4.6 post acne erythema images and scores of Cream base group by ANTERA 3D® camera of subject No.17

Table 4.19 Post inflammatory hyperpigmentation score in acne area from ANTERA 3D® camera

Subject No.	Right							Left						
	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	0.55	0.548	0.573	0.571	0.592	0.559	0.585	0.59	0.545	0.586	0.565	0.592	0.629	0.589
2	0.578	-	-	-	-	-	-	0.544	-	-	-	-	-	-
3	0.502	0.539	0.528	0.529	0.536	0.541	0.521	0.526	0.574	0.545	0.546	0.556	0.561	0.558
4	0.647	0.682	0.614	0.612	0.591	0.601	0.611	0.627	0.646	0.619	0.612	0.597	0.612	0.61
5	0.526	0.529	0.553	0.572	0.569	0.575	0.569	0.523	0.527	0.548	0.547	0.564	0.564	0.564
6	0.525	0.541	0.557	0.542	0.537	0.539	0.522	0.536	0.537	0.548	0.554	0.553	0.561	0.548
7	0.587	0.579	0.545	0.58	0.577	0.596	0.568	0.558	0.567	0.521	0.545	0.563	0.565	0.563
8	0.448	0.514	0.523	-	-	-	-	0.458	0.527	0.549	-	-	-	-
9	0.454	0.442	0.439	0.43	0.436	0.417	0.441	0.442	0.447	0.447	0.43	0.455	0.462	0.444
10	0.44	0.413	0.481	0.456	0.42	0.408	0.418	0.422	0.44	0.445	0.419	0.41	0.434	0.428
11	0.549	0.532	0.558	0.565	-	-	-	0.554	0.579	0.578	0.568	-	-	-
12	0.496	-	-	-	-	-	-	0.52	-	-	-	-	-	-
13	0.563	0.526	0.54	0.566	0.532	0.528	0.495	0.515	0.491	0.496	0.49	0.466	0.468	0.464
14	0.446	0.459	0.461	0.49	0.49	0.453	0.475	0.43	0.426	0.432	0.449	0.443	0.454	0.456
15	0.405	0.405	0.418	0.407	0.396	0.396	0.444	0.411	0.396	0.409	0.404	0.409	0.414	0.416
16	0.498	0.487	0.502	0.509	0.518	0.522	0.519	0.497	0.49	0.499	0.496	0.505	0.515	0.513
17	0.46	0.448	0.449	0.475	0.445	0.461	0.427	0.405	0.407	0.415	0.426	0.449	0.442	0.442

18	0.429	0.416	0.42	0.443	0.431	0.432	0.447	0.452	0.459	0.464	0.466	0.473	0.463	0.468
19	0.462	0.446	0.447	0.466	0.461	0.489	0.506	0.454	0.445	0.459	0.459	0.464	0.498	0.504
20	0.418	0.403	0.439	0.443	0.47	0.459	0.449	0.399	0.41	0.442	0.457	0.465	0.473	0.48
21	0.454	0.453	0.471	0.455	0.481	0.472	0.454	0.477	0.495	0.496	0.489	0.487	0.474	0.485

Table 4.19 demonstrates post inflammatory hyperpigmentation score by ANTERA 3D® camera of all subjects in each visit. The ANTERA 3D images was taken at both cheeks of all subjects at baseline, week 2, week 4, week 6, week 8, week 10 and week 12 and measured area with acne seen. The statistical analysis was evaluated to compare between Niacinamide group and cream base group at baseline, week 2, week 4, week 6, week 8, week 10 and week 12. Mean of post inflammatory hyperpigmentation score was not statistical difference at the beginning and slightly increased in both groups as shown in **Table 4.20** and **Figure 4.6.**

According to **Table 4.21** and **Table 4.22,** it is shown that post inflammatory hyperpigmentation score in acne skin slightly decreased in Niacinamide group with no statistically difference from baseline in every follow-up visit compare to Cream base group which increased significantly since week 6 (p =0.02). The change in inflammatory lesion counts at week 12 was increased 1% and 4% from baseline in Niacinamide group and cream base group respectively. But the change between 2 groups were not statistically difference. (P=0.16)

Table 4.20 Post inflammatory hyperpigmentation score in acne area at baseline, week 2, week 4, week 6, week 8, week 10, week 12 compared between Niacinamide group and cream base group

Time	Treatment Group	N	mean	SE	Co ef.	Lower 95%	Upper 95%	P value
Baseline	Niacinamide Cream base	21	0.5 0.489	0.014 0.014	0.011	-0.026	0.027	0.05
Week2	Niacinamide Cream base	19	0.494 0.493	0.016 0.016	0.003	-0.034	0.04	0.87
Week4	Niacinamide Cream base	19	0.502 0.499	0.013 0.015	0.004	-0.033	0.041	0.68
Week6	Niacinamide Cream base	18	0.502 0.5	0.014 0.015	0.003	-0.034	0.04	0.72
Week8	Niacinamide Cream base	17	0.5 0.496	0.015 0.016	0.004	-0.033	0.041	0.43
Week10	Niacinamide Cream base	17	0.505 0.498	0.016 0.015	0.006	-0.031	0.043	0.37
Week12	Niacinamide Cream base	17	0.498 0.5	0.014 0.014	-0.003	-0.04	0.342	0.65

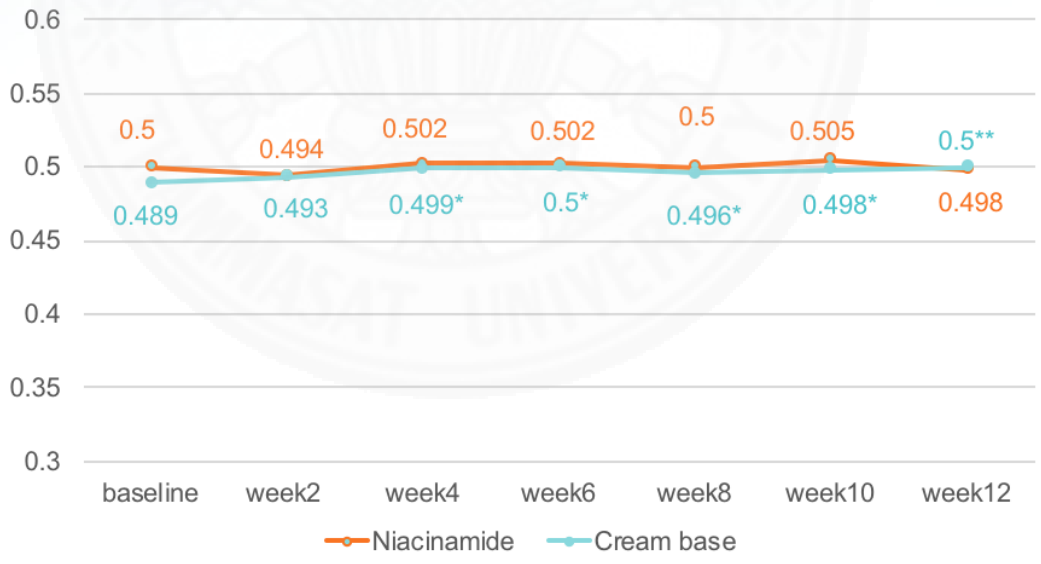


Figure 4.7 Graph of post-inflammatory hyperpigmentation score of acne skin

Table 4.21 Post inflammatory hyperpigmentation score change from baseline in acne skin area in each visit

Time	Niacinamide	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	0.0004	-0.012	0.013	0.95
Wk4	-0.006	-0.019	0.006	0.28
Wk6	-0.005	-0.015	0.005	0.34
Wk8	-0.006	-0.021	0.009	0.42
Wk10	-0.01	-0.024	0.004	0.15
Wk12	-0.003	-0.019	0.012	0.58
Time	Cream base	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	0.007	-0.018	0.003	0.17
Wk4	0.013	-0.02	0.000	0.05
Wk6	0.012	-0.02	-0.002	0.02
Wk8	0.012	-0.026	0.026	0.09
Wk10	0.017	0.005	0.028	0.06
Wk12	0.02	0.009	0.031	0.04

Table 4.22 Post inflammatory hyperpigmentation score change in acne skin area from baseline (%) to week 12

Treatment	Mean	P value
Niacinamide	1	0.06
Cream base	4	

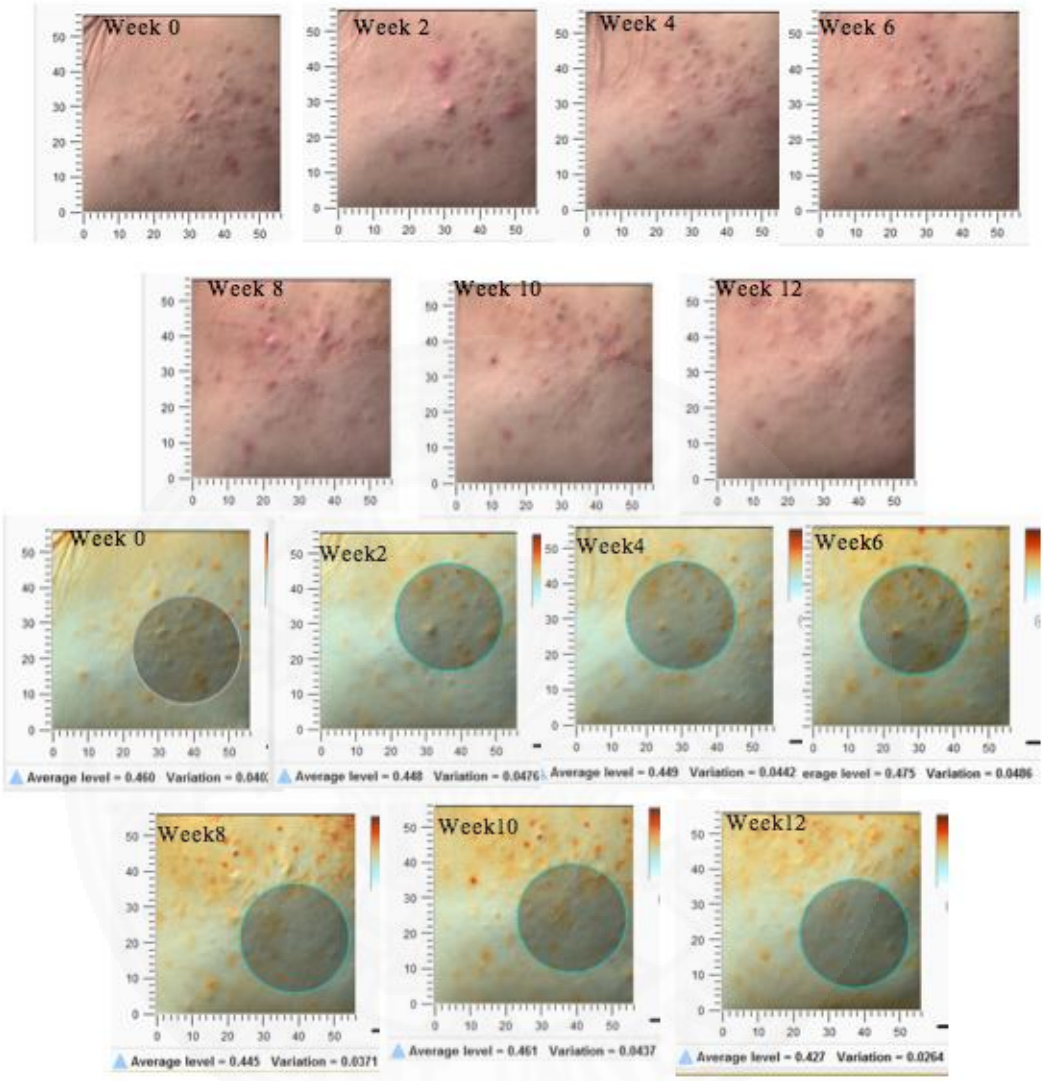


Figure 4.8 Post inflammatory hyperpigmentation images and scores of Niacinamide group by ANTERA 3D® camera of subject No.17

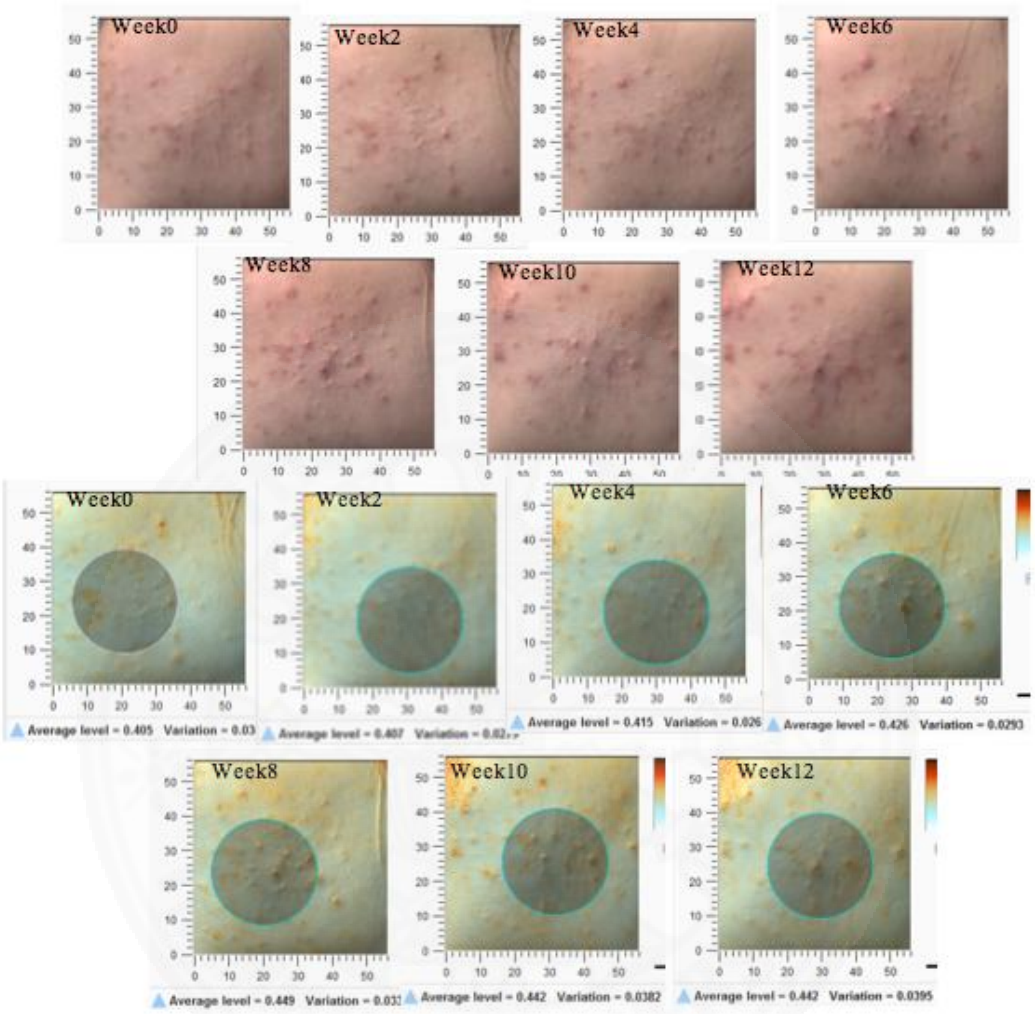


Figure 4.9 Post inflammatory hyperpigmentation images and scores of cream base group by ANTERA 3D® camera of subject No.17

Table 4.23 Post inflammatory hyperpigmentation score in normal skin area from ANTERA 3D® camera

Subject No.	Right							Left						
	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	0.64	0.637	0.643	0.65	0.66	0.622	0.665	0.665	0.658	0.661	0.676	0.689	0.703	0.639
2	0.593	-	-	-	-	-	-	0.603	-	-	-	-	-	-
3	0.542	0.548	0.536	0.533	0.562	0.564	0.606	0.484	0.498	0.508	0.483	0.517	0.515	0.52
4	0.677	0.617	0.647	0.637	0.647	0.639	0.65	0.75	0.735	0.727	0.678	0.681	0.687	0.672
5	0.528	0.542	0.563	0.528	0.543	0.559	0.555	0.526	0.542	0.49	0.539	0.572	0.529	0.546
6	0.564	0.547	0.588	0.552	0.564	0.575	0.557	0.529	0.54	0.548	0.546	0.548	0.549	0.543
7	0.565	0.575	0.503	0.551	0.562	0.587	0.581	0.564	0.601	0.552	0.569	0.572	0.585	0.582
8	0.487	0.54	0.555	-	-	-	-	0.502	0.532	0.584	-	-	-	-
9	0.491	0.463	0.473	0.446	0.457	0.445	0.472	0.473	0.457	0.46	0.462	0.472	0.467	0.475
10	0.446	0.471	0.457	0.444	0.435	0.45	0.456	0.426	0.448	0.439	0.462	0.443	0.445	0.471
11	0.561	0.598	0.564	0.582	-	-	-	0.59	0.629	0.598	0.604	-	-	-
12	0.464	-	-	-	-	-	-	0.465	-	-	-	-	-	-
13	0.521	0.534	0.506	0.493	0.49	0.491	0.474	0.547	0.512	0.536	0.505	0.49	0.483	0.493
14	0.414	0.403	0.411	0.447	0.448	0.463	0.442	0.436	0.435	0.473	0.468	0.444	0.501	0.438
15	0.439	0.415	0.419	0.418	0.424	0.425	0.445	0.449	0.425	0.437	0.419	0.449	0.46	0.458
16	0.478	0.502	0.496	0.484	0.512	0.532	0.518	0.514	0.497	0.529	0.554	0.504	0.533	0.517

17	0.387	0.378	0.367	0.391	0.449	0.411	0.415	0.456	0.443	0.431	0.482	0.458	0.492	0.452
18	0.444	0.437	0.44	0.441	0.431	0.468	0.483	0.444	0.447	0.448	0.458	0.44	0.42	0.465
19	0.546	0.56	0.523	0.515	0.517	0.56	0.578	0.557	0.531	0.516	0.523	0.562	0.568	0.563
20	0.483	0.508	0.491	0.533	0.513	0.505	0.507	0.453	0.467	0.484	0.499	0.531	0.521	0.496
21	0.496	0.494	0.539	0.512	0.552	0.487	0.498	0.458	0.441	0.481	0.489	0.475	0.445	0.475

Table 4.23 demonstrates post inflammatory hyperpigmentation score in normal skin by ANTERA 3D® camera of all subjects in each visit. The ANTERA 3D images was taken at both cheeks of all subjects at baseline, week 2, week 4, week 6, week 8, week 10 and week 12 and chose to measure area with no acne seen.

According to **Table 4.24,** it is shown that post inflammatory hyperpigmentation score in normal skin slightly increased in both groups with no statistically difference from baseline in every follow-up visit.

Table 4.24 Post inflammatory hyperpigmentation score change from baseline in normal skin area in each visit

Time	Niacinamide	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	0.001	-0.011	0.014	0.82
Wk4	-0.001	-0.015	0.013	0.88
Wk6	0.003	-0.011	0.016	0.68
Wk8	0.009	-0.007	0.026	0.25
Wk10	0.007	-0.007	0.021	0.34
Wk12	0.008	-0.004	0.204	0.18
Time	Cream base	Lower 95%	Upper95%	P value
Wk0	0	-	-	-
Wk2	0.002	-0.078	0.013	0.62
Wk4	0.006	-0.082	0.019	0.39
Wk6	-0.001	-0.016	0.014	0.89
Wk8	0.004	-0.013	0.012	0.64
Wk10	0.01	-0.008	0.03	0.26
Wk12	0.01	-0.008	0.029	0.24

4.3 Evaluation of satisfaction

The satisfactory evaluation was done by doctor and patients at every follow-up visit in week 2, week 4, week 6, week8, week 10 and week 12. The scales were rated as “0” means no change, “1” means slight improvement, “2” means moderate improvement, “3” means significant improvement and “4” means excellent improvement.

Table 4.25 Physician improvement scale

Subject No.	**Niacinamide**						**Cream base**					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	0	2	3	4	4	1	0	1	2	3	4	2
2	-	-	-	-	-	-	-	-	-	-	-	-
3	0	3	3	3	2	4	1	3	3	3	3	4
4	1	3	3	3	3	4	1	3	3	3	4	3
5	2	1	1	2	3	4	2	1	1	1	2	4
6	1	1	2	2	2	4	1	1	2	2	2	4
7	1	2	3	2	2	2	2	2	2	2	3	3
8	1	2	-	-	-	-	0	2	-	-	-	-
9	1	2	1	3	3	4	1	2	2	3	3	4
10	1	1	2	2	3	3	1	1	2	2	3	3
11	2	2	3	-	-	-	1	1	3	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-

13	2	2	3	3	4	4	2	1	2	3	3	3
14	2	1	2	1	1	3	2	1	2	2	1	4
15	1	2	3	3	3	4	1	2	2	2	1	4
16	1	1	1	3	2	1	1	1	1	2	2	1
17	1	2	1	1	3	4	1	2	0	1	1	3
18	0	3	3	3	3	4	0	3	3	3	3	4
19	1	3	3	3	3	4	1	2	3	3	3	4
20	0	1	2	3	3	4	1	1	2	2	3	4
21	1	2	3	3	3	3	1	1	2	3	3	3

According to **Table 4.23** shows all physician improvement scale in each follow-up visit. 0 = no improvement, 1= Slight improvement, 2= Moderate improvement, Significant improvement and 4 = Excellent improvement. And the statistical analysis in **Table 4.24** compared percentage of each level of physician improvement scale between 2 groups. The percentage of significant improvement and excellent improvement were increased by the end of week 12 in both groups. However, there were no statistical significant differences in every follow-up visit between 2 groups.

Table 4.26 Statistical analysis of physician improvement scale at each visit compare between Niacinamide group and cream base group

Variables	**Niacinamide**	**Cream base**	**p-value**
	N (%)	**N (%)**	
Week2			
0	4(21%)	3(16%)	1
1	11(58%)	12(63%)	
2	4(21%)	4(21%)	
Week4			
1	6(32%)	10(53%)	1
2	9(47%)	6(32%)	
3	4(21%)	3(16%)	
Week 6			
0	0(0%)	1(6%)	0.09
1	4(22%)	2(11%)	
2	4(22%)	10(56%)	
3	10(56%)	5(28%)	
Week 8			
1	2(12%)	2(12%)	0.7
2	4(24%)	4(24%)	
3	10(59%)	10(59%)	
4	1(3%)	1(6%)	
Week 10			
1	1(6%)	3(18%)	0.9
2	4(24%)	3(18%)	
3	10(59%)	9(53%)	
4	2(12%)	2(12%)	
Week 12			
2	2(12%)	3(18%)	0.9
3	7(41%)	11(65%)	
4	8(47%)	3(18%)	

The results were grouped into little to no improvement (0-1) and improvement (2-4) as shown in **Table 4.25**. After 12 weeks of treatment all patients

had improvement. However, there were still no statistical significant differences in every follow-up visit between 2 groups.

Table 4.27 Statistic analysis of improvement by physician at each visit compare between Niacinamide group and cream base group

Variables	**Niacinamide**	**Cream base**	**p-value**
	N (%)	**N (%)**	
Week2			
0-1	15(79%)	15(79%)	0.65
2-4	4(21%)	4(21%)	
Week4			
0-1	6(32%)	10(53%)	0.16
2-4	13(68%)	9(47%)	
Week 6			
0-1	4(22%)	3(17%)	0.67
2-4	14(78%)	15(83%)	
Week 8			
0-1	2(12%)	2(12%)	1
2-4	15(88%)	15(88%)	
Week 10			
0-1	1(6%)	3(18%)	0.29
2-4	16(94%)	14(82%)	
Week 12			
0-1	0	0	-
2-4	17(100%)	17(100%)	

Table 4.28 Patient satisfaction index

Subject No.	**Niacinamide**						**Cream base**					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	1	2	3	4	2	1	1	1	2	3	3	2
2	-	-	-	-	-	-	-	-	-	-	-	-
3	0	3	4	4	3	4	1	3	3	4	4	4
4	3	3	3	3	3	4	3	4	4	4	4	3
5	2	0	2	2	4	4	1	1	2	1	4	4
6	1	1	1	2	3	4	1	2	2	2	3	4
7	2	2	2	2	2	2	2	2	2	3	3	3
8	2	2	-	-	-	-	2	2	-	-	-	-
9	3	3	2	3	3	4	3	3	3	4	3	4
10	0	1	2	2	3	3	1	2	2	2	3	3
11	3	3	4	-	-	-	1	0	4	-	-	-
12	-	-	-	-	-	-	-	-	-	-	-	-
13	3	4	3	4	4	4	2	3	3	4	4	3
14	1	1	1	1	1	3	2	2	3	2	2	4
15	2	2	3	3	4	4	1	1	2	3	3	4
16	0	1	1	1	1	1	0	1	1	1	1	1
17	1	3	1	1	4	4	4	3	0	1	2	3

18	0	3	4	3	4	4	0	2	4	3	4	4
19	4	3	4	3	3	4	1	3	4	3	3	4
20	0	1	2	4	4	4	1	2	2	4	4	4
21	1	2	2	3	2	3	1	1	2	3	2	3

According to **Table 4.28** shows all patient satisfaction index in each follow-up visit. 0 = no improvement, 1= Slight improvement, 2= Moderate improvement, Significant improvement and 4 = Excellent improvement. And the statistical analysis in **Table 4.29** compared percentage of each level of patient satisfaction index between 2 groups. The percentage of excellent improvement was increased by the end of week 12 in both groups. However, there were no statistical significant differences in every follow-up visit between 2 groups

Table 4.29 Statistical analysis of patient satisfaction index at each visit compare between Niacinamide group and cream base group

Variables	Niacinamide	Cream base	p-value
	N (%)	N (%)	
Week2			0.46
0	5(26%)	3(10%)	
1	5(26%)	10(53%)	
2	4(21%)	4(21%)	
3	4(21%)	2(11%)	
4	1(5%)	1(5%)	
Week4			
0	1(5%)	1(5%)	0.98
1	5(26%)	5(26%)	
2	5(26%)	5(26%)	
3	7(37%)	7(37%)	
4	1(5%)	1(5%)	
Week 6			
0	0(0%)	1(5%)	0.62
1	4(22%)	1(5%)	
2	6(33%)	8(44%)	
3	4(22%)	4(22%)	
4	4(22%)	4(22%)	
Week 8			
1	3(18%)	3(18%)	1
2	4(24%)	3(18%)	
3	6(35%)	6(35%)	
4	4(24%)	5(29%)	
Week 10			
1	2(12%)	1(5%)	1
2	3(18%)	3(18%)	
3	6(35%)	7(41%)	
4	6(35%)	6(35%)	
Week 12			
1	2(12%)	1(5%)	0.77
2	1(6%)	1(5%)	

3	3(18%)	6(35%)	
4	11(65%)	9(53%)	

The results were grouped into little to no improvement (0-1) and improvement (2-4) as shown in **Table 4.28**. After 12 weeks of treatment most patients (>80%) experienced improvement. However, there were still no statistical significant differences in every follow-up visit between 2 groups.

Table 4.30 Statistic analysis of improvement by patients at each visit compare between Niacinamide group and cream base group

Variables	**Niacinamide**	**Cream base**	**p-value**
	N (%)	**N (%)**	
Week2			
0-1	10(53%)	12(63%)	0.511
2-4	9(47%)	7(37%)	
Week4			
0-1	6(32%)	6(32%)	1
2-4	13(68%)	13(68%)	
Week 6			
0-1	4(22%)	2(11%)	0.37
2-4	14(78%)	16(89%)	
Week 8			
0-1	3(18%)	3(18%)	1
2-4	14(82%)	14(82%)	
Week 10			
0-1	2(12%)	1(6%)	0.55
2-4	15(88%)	16(94%)	
Week 12			
0-1	2(12%)	1(6%)	0.55
2-4	15(88%)	16(94%)	

4.4 Side effects

In every follow-up visit, the patients were asked if they had itching, burning, crusting, greasy skin, dermatitis or not. The data is shown in **Table 4.31, Table 4.32, Table 4.33, Table 4.34** and **Table 4.35.**

Table 4.31 Itching of Niacinamide group and cream base group at each follow-up visit

Subject No.	**Niacinamide**						**Cream base**					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	+	-	-	-	-	-	+	-	-	-	-	-
2												
3	-	+	+	+	+	-	-	+	+	+	+	-
4	-	-	+	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-
7	+	-	-	-	-	-	-	-	-	-	-	-
8	+	+					-	+				
9	-	+	-	-	-	-	+	+	-	+	-	-
10	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-				-	-	-			
12												

13	-	-	-	-	-	-	+	-	-	-	-	-
14	-	-	-	-	+	-	-	-	-	-	+	-
15	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	-	-	-	-	-
20	+	-	-	-	-	-	+	-	-	-	-	-
21	-	-	-	-	-	-	-	-	-	-	-	-

+ present, - absent

Table 4.32 Burning of Niacinamide group and cream base group at each follow-up visit

Subject No.	**Niacinamide**						**Cream base**					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	+	-	+	-	-	-	+	+	-	-	-	-
2												
3	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	+	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-					-	-				
9	+	-	-	-	-	-	+	-	-	-	-	-
10	-	+	-	-	-	-	-	+	-	-	-	-
11	-	-	-				-	-	-			
12												
13	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	+	-	-	-	-	-	+	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	-	-	-	-	-	-	-	-	-	-
17	+	-	-	-	-	-	+	-	-	-	-	-

18	-	-	-	-	-	-	-	-	-	-	-	-
19	+	-	-	-	-	-	+	-	-	-	-	-
20	+	-	-	-	-	-	+	-	-	-	-	-
21	-	-	-	-	-	-	-	-	-	-	-	-

+ present, - absent

Table 4.33 Crusting of Niacinamide group and cream base group at each follow-up visit

Subject No.	Niacinamide						Cream base					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	-	+	-	-	-	-	-	+	-	-	-	-
2												
3	-	-	+	-	-	-	-	-	-	-	-	-
4	-	-	+	-	-	-	-	-	+	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	+	-	-	-	-	-	+	-	-	-
7	+	-	-	-	-	-	-	-	-	-	-	-
8	+	-					+	-				
9	+	+	+	+	+	-	+	+	-	-	-	-
10	-	-	+	-	-	-	-	-	+	-	-	-
11	-	-	-				-	-	-			
12												
13	+	-	-	-	-	-	+	-	-	-	-	-
14	-	-	-	-	-	-	-	+	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-
16	-	+	-	-	-	-	-	+	-	-	-	-
17	-	+	-	+	-	-	-	+	-	-	-	-

18	-	-	-	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	-	-	-	-	-	-	-
20	-	-	-	-	-	-	-	-	-	-	-	-
21	-	+	-	-	-	-	-	+	-	-	-	-

+ present, - absent

Table 4.34 Greasiness of skin of Niacinamide group and cream base group at each follow-up visit

Subject No.	Niacinamide						Cream base					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	-	-	+	-	+	-	-	-	+	-	+	-
2												
3	-	-	-	-	-	-	-	-	-	-	-	-
4	+	-	-	+	+	+	-	-	-	-	+	+
5	-	-	-	+	-	-	-	-	-	+	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-					-	-				
9	+	+	-	+	+	-	+	+	-	-	+	-
10	+	-	+	-	+	-	+	-	+	-	+	-
11	+	-	+				+	-	+			
12												
13	-	+	+	+	+	+	-	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+	+
15	+	-	+	-	-	-	+	-	+	-	-	-
16	+	+	+	+	+	+	+	+	+	+	+	+
17	-	-	-	-	-	-	-	-	-	-	-	-

18	-	+	+	+	+	+	-	+	+	+	+	+
19	-	+	-	-	-	-	-	+	-	-	-	-
20	-	+	+	-	-	-	-	+	+	-	-	-
21	-	+	+	-	-	-	-	+	+	-	-	-

+ present, - absent

Table 4.35 Dermatitis of Niacinamide group and cream base group at each follow-up visit

Subject No.	Niacinamide						Cream base					
	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
1	-	-	-	-	-	-	-	-	-	-	-	-
2												
3	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-
6	+	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-					-	-				
9	+	-	+	+	-	+	+	-	+	-	-	+
10	-	-	-	-	-	-	-	-	-	-	-	+
11	-	-	-				+	-	-			
12												
13	-	-	-	-	-	-	-	-	-	-	-	-
14	+	-	-	-	-	-	+	-	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	-	-	-	-	-	-	-	-	-	-
17	+	-	+	-	-	-	+	-	-	-	-	-

18	-	-	-	-	-	-	-	-	-	-	-	-
19	+	-	-	-	-	-	+	-	-	-	-	-
20	+	-	-	-	-	-	+	-	-	-	-	-
21	-	-	-	-	-	-	-	-	-	-	-	-

+ present, - absent

Table 4.36 Statistical analysis of side effects compare between 2 groups at each follow-up visit

variables	Niacinamide N (%)	Cream base N (%)	P-value
Week2			
Itching	4(21%)	4(21%)	1
Burning	5(26%)	5(26%)	1
Crusting	4(21%)	3(16%)	1
Greasy skin	7(37%)	6(32%)	0.73
Dermatitis	6(31%)	6(31%)	1
Week4			
Itching	3(16%)	3(16%)	1
Burning	1(5%)	2(10%)	1
Crusting	5(26%)	6(32%)	0.721
Greasy skin	8(42%)	8(42%)	1
Dermatitis	0(0%)	0(0%)	-
Week6			
Itching	2(11%)	1(5%)	1
Burning	2(11%)	0(0%)	0.49
Crusting	5(28%)	4(22%)	1
Greasy skin	10(56%)	10(56%)	1

Dermatitis	2(11%)	1(6%)	1
Week8			
Itching	1(6%)	2(11%)	1
Burning	1(6%)	1(6%)	1
Crusting	2(11%)	0(0%)	0.49
Greasy skin	7(41%)	5(29%)	0.47
Dermatitis	1(6%)	0(0%)	1
Week10			
Itching	2(12%)	2(12%)	1
Burning	0(0%)	0(0%)	0
Crusting	1(6%)	0(0%)	1
Greasy skin	8(47%)	8(47%)	1
Dermatitis	0(0%)	0(0%)	-
Week12			
Itching	0(0%)	0(0%)	-
Burning	0(0%)	0(0%)	-
Crusting	0(0%)	0(0%)	-
Greasy skin	5(29%)	5(29%)	1
Dermatitis	1(6%)	2(11%)	1

According to **Table 4.36** found that patients in both groups experienced itching, burning, crusting, greasy skin and dermatitis. No statistically significant different in side effects between both groups during 12 weeks.

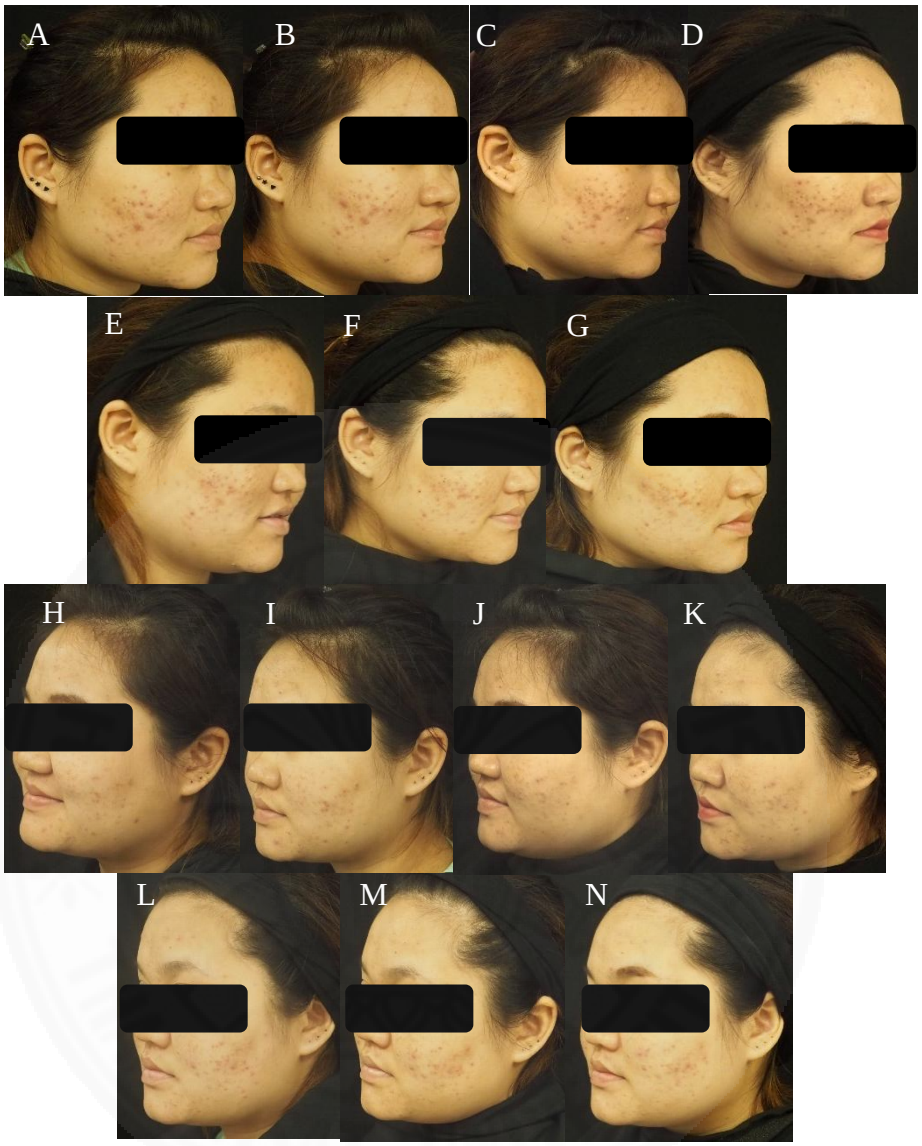


Figure 4.10 Clinical photos of Niacinamide treated group (A-G) compare with cream base group (H-N)

CHAPTER 5
DISCUSSION AND CONCLUSION

5.1 Discussion

The main pathogenesis of acne vulgaris composed of 4 factors including follicular epidermal hyperproliferation, increase sebum production, presence of *P.acnes* and inflammation. Currently, the evidence for topical medications aim at sebum production and inflammation are still limited. And the available topical medications now have some undesirable side effects.

There are several previous studies about topical Niacinamide in the treatment of facial acne vulgaris. First study was from Shalita et al [54] in 1995. It was a double-blind, randomized, parallel study compared efficacy of 4% Niacinamide gel against 1% clindamycin gel. Seventy-six patients with moderate inflammatory acne vulgaris were randomized to apply 4% Niacinamide gel or 1% clindamycin gel twice daily for 8 weeks. They found both treatments had comparable (p=0.19) efficacy by using Physician's Global Evaluation of Inflammatory acne (patients with improved condition were 86% and 68% in Niacinamide group and clindamycin group respectively). Later in 2013 Shahmoradi et al[105] used higher concentration of Niacinamide to perform randomized, controlled clinical trial. They compared 5% Niacinamide with 2% clindamycin in 60 female patients with mild or moderate acne vulgaris for 8 weeks. Result clearly showed acne severity index (calculated by using number of papules, pustules and comedone) was decreased from baseline significantly but no statistically significant between Niacinamide group and clindamycin groups. They concluded that 5% Niacinamide was at least as effective as 2% clindamycin for treatment of mild to moderate acne vulgaris. Other studies in the past they compared in combination therapy with 4% Niacinamide plus clindamycin and clindamycin alone[103],[150] found no difference in efficacy of both clindamycin and its combination with Niacinamide. One is from Dos et al.[103] Eighty patients with moderate acne vulgaris were enrolled. Forty patients received 1% clindamycin and another 40 patients received 1% clindamycin plus 4% Niacinamide twice daily for 6 weeks. The acne improvement was graded. They found 40% excellent response, 50%

good response and 10% fair response in clindamycin group. And combination group found 50% excellent response, 45% good response and 5% fair response. There was no significant difference in response between the two groups. Another study carried out by Sardesai et al. [150] A total of 75 patients with inflammatory acne vulgaris were divided into 3 groups. Group A received 4% Niacinamide plus 1% clindamycin. Group B received 1% clindamycin. Group C was resistance to topical antibiotics and also received combination drug for 8 weeks. They concluded that addition of Niacinamide was not as much worthy as in treating inflammatory acne compared to clindamycin alone and combination treatment did not help much in relieving of resistant acne.

Our study was conducted in 21 patients with mild to moderate facial acne vulgaris. The follow up duration was longer up to 12 weeks compared to previous studies which ranged from 6-8 weeks. A 5% Niacinamide was used which was high concentration same as Shahmoradi et al[105]. Furthermore, we combined topical 2.5% Benzoyl peroxide with 5% Niacinamide to cover 4 basic pathogenesis of acne and compared with 2.5% Benzoyl peroxide plus cream base. We evaluated efficacy by using clinical study (acne lesion count) and also biometric assessment including sebum casual level by Sebumeter® and post inflammatory erythema and post inflammatory hyperpigmentation by ANTERA® 3D camera analysis. Additionally, there were satisfaction assessment by doctor and patients and side effects evaluation using questionnaire which can provide more information about topical 2.5% Benzoyl peroxide with 5% Niacinamide in the treatment of facial acne vulgaris.

Our results were similar to previous studies. We found both non-inflammatory lesion counts and inflammatory lesion counts decreased significantly in the end of study from baseline. But reduction of inflammatory lesions count was not significant difference between Niacinamide group (2.5% Benzoyl peroxide + 4% Niacinamide) and cream base group (2.5% Benzoyl peroxide + cream base). Interestingly, at the end of the study we found more reduction of non-inflammatory lesion counts in Niacinamide group than in cream base group (51% and 31% respectively). And it was a statistical significant reduction ($p=0.004$).

Moreover, there are some previous study by Draelos et al [6] about Niacinamide in reduction of sebum, which is one of pathogenic factor of acne. They found that in 6 weeks 2% Niacinamide may be effective in reducing sebum excretion

rate significantly in Japanese individual and casual sebum level in Caucasian individuals. It was thought that Niacinamide induce exfoliation within the duct connecting the sebaceous gland to the skin surface and encourage sebum flow to the skin surface faster leaded to depletion of the reservoir of sebum in the duct. So, it decreases sebum excretion from the skin. Another study used viable human facial biopsies from face-lift surgery to measure the effect of Niacinamide on sebaceous lipogenesis. They found that Niacinamide significantly reduced in total lipogenesis and produced marked reductions in triglyceride which represents 50-60% of sebaceous gland lipids. [70] In our study, sebum casual level of Niacinamide group started to decrease significantly from baseline in 6 weeks and continue to reduce in every follow up visit after that which was faster and more sustainable than in cream base group that decreased significant only at week 8 and week 12. But at the end of 12 weeks both group shows significant reduction in sebum casual level with no statistically difference between 2 groups. This could be from Benzoyl Peroxide. As in previous studied of Schmidt et al[151] shown Benzoyl peroxide may affect sebum excretion rate in some patients. They found 20% of patients had increased sebum excretion rate, 70% of patients decreased in sebum excretion rate and 10% had no change compared to placebo gel after 6 weeks.

Niacinamide is hypothesized to reduce acne because it has anti-inflammatory effect by inhibiting Propionibacterium acnes-induced IL-8 production in keratinocytes through NF-kB and MAPK pathways.[77, 152] In our study evaluated post acne erythema which should be decreased due to decrease inflammation. We found the hemoglobin index by ANTERA® 3D camera was slightly decreased in Niacinamide group in contrast to cream base group that slightly increased. However, there was no statistical difference from baseline and between 2 groups. The reduction of inflammation might not be seen clearly in clinical or the evaluation should be done after the disease subsided and no new active lesions.

Niacinamide can reduce hyperpigmentation by inhibiting melanosome transfer in vitro and also clinically significant improved hyperpigmentation such as melasma, freckles and lentigines in 4 weeks.[9] Other studies used topical combination therapy such as study from Kimball et al [121] was 4% Niacinamide with 2% N-acetyl glucosamine formulation and study from Do Hyun Lee et al[153] was 2% Niacinamide

with 2% Tranexamic acid also shown significant improvement in facial hyperpigmentation, mostly solar lentigines, in 8 weeks. So, we also study on post-inflammatory hyperpigmentation from acne by using ANTERA® 3D camera analysis found little increment in melanin index at the end of 12 weeks in both treatment groups. This may be due to different nature of disease between acne vulgaris with post inflammatory hyperpigmentation and other pigmentary disorders in the previous studies. Because acne vulgaris is chronic inflammatory disease and can cause new post-inflammatory hyperpigmentation. Furthermore, our study also evaluated melanin index at normal skin on both treatment groups because we started our protocol at late winter to early summer. Sun exposure might also play a role in increased skin pigmentation. We found increment in both sides with no statistical significant. As a result, in our study the hyperpigmentation from acne increased 1% in Niacinamide group but not statistically significant different from baseline in contrast to Cream base group which the hyperpigmentation increased 4% with statistically significant from baseline. Niacinamide might play a role in reduction of post inflammatory hyperpigmentation. But further study should be done in same season with more participants and include only participants with post inflammatory hyperpigmentation with minimal to no active acne could be done to definite this.

In this study, we also evaluated acne improvement by using physician improvement scale shows good clinical response. There was 41% significant improvement and 47% excellent improvement in Niacinamide group. In Cream base group found 65% significant improvement and 18% excellent improvement but there was no difference between Niacinamide group and cream base group. This result is in the same direction of Sardesai et al's study[150], they combined 4% Niacinamide with1% clindamycin and evaluated results by using physician's global evaluation found that 50% in combination group show moderate response and in clindamycin alone showed 44.8% moderate response and also no difference between 2 groups. Additionally, our study also evaluated patient satisfaction and found good result of acne improvement assessed by patients. At the end of study showed 65% and 53% excellent improvement in Niacinamide group and cream base group respectively. However, there was no statistical difference between 2 groups.

Considering the questionaire evaluation on side effect including itchiness, burning, crusting, greasiness and dermatitis. Most of them reports no discomfort. A few had itchy, burning, crusting, greasy skin and dermatitis but tended to decrease in the end of treatment in both treatment groups and there was no statistical significant difference between groups. Similar to previous study [96] which patients experienced minimal side effects such as itching, burning, crusting, sense of greasiness, contact dermatitis and no major adverse effects. However, studies about long term side effects are needed to determine profile side effects of topical Niacinamide.

To sum up, Combination of 2.5% Benzoyl peroxide with 5% Niacinamide is more effective in the treatment of mild to moderate facial acne vulgaris in reducing non-inflammatory lesions and faster improvement of acne lesions and facial sebum reduction than 2.5% Benzoyl peroxide with cream base with minimal side effects. But its efficacy in inflammatory lesions, post acne erythema and post-inflammatory hyperpigmentation is comparable to 2.5% Benzoyl peroxide with cream base. Nevertheless, there were some limitations of this study including small sample size and some loss follow-up patients.

5.2 Conclusion

The combination of 2.5% benzoyl peroxide with 5% Niacinamide is found to be more effective in the treatment of mild to moderate facial acne vulgaris, since it was found to reduce non-inflammatory lesions and more quickly improve non-inflammatory lesions and facial sebum reduction compared to 2.5% benzoyl peroxide with a cream base. It also had minimal side effects. However, the efficacy of 2.5% benzoyl peroxide with 5% Niacinamide at treating inflammatory lesions, post acne erythema, and post-inflammatory hyperpigmentation is comparable to 2.5% benzoyl peroxide with a cream base.

5.3 Recommendations

5.3.1 Recommendation for clinical application

5.3.1.1 Niacinamide is an additional topical medication for mild to moderate facial acne vulgaris for better reduction of non-inflammatory lesions and faster result with little side effects.

5.3.2 Recommendation for future research

5.3.2.1 Further studies with a larger number of participants may provide the better precision and accuracy.

5.3.2.2 Further study with difference concentration of Niacinamide could be done to optimize an efficacy of the treatment.

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APPENDICES

APPENDIX A
ABSTRACT FOR PROCEEDING

Clinical Comparison Between Topical 2.5%Benzoyl Peroxide + 5% Niacinamide and 2.5%Benzoyl Peroxide in Reducing Facial Pore Size of Patients with Facial Acne Vulgaris

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Abstract

Background: Topical Niacinamide or Nicotinamide is an amide of vitaminB3(niacin) which widely used in cosmetic preparations. It can help improving acne lesions and also can reduce facial sebum production but reducing facial pore size property is await to be proven.

Objective: To evaluate and compare clinical efficacy between topical 2.5% Benzoyl peroxide + 5% Niacinamide and 2.5% Benzoyl peroxide in reducing pore size of patients with mild to moderate facial acne vulgaris.

Methods: Patient with mild to moderate facial acne vulgaris, aged 18 to 40 years were enrolled. The treatment was randomly assigned to left or right side of face in an individual participant. One side received topical 2.5% Benzoyl peroxide + 5% Niacinamide and another side received only topical 2.5%Benzoyl peroxide for 4 weeks. The pore size was assessed by ANTERA 3D camera at 2nd week and 4th week.

Results: The mean pore size in Niacinamide group (2.5% Benzoyl peroxide + 5% Niacinamide) was decreased from 0.895 to 0.827 mm^3 and in cream base group (2.5%Benzoyl peroxide + cream base) was increased from 0.767 to 0.777 mm^3. The percentages change from baseline were decreased in both group, 28% and 18% in Niacinamide group and cream base group respectively but there was no statistically difference between two groups (P=0.225).

Conclusion: Combination of topical 2.5% Benzoyl peroxide + 5% Niacinamide tends to be more effective than topical 2.5% Benzoyl peroxide in pore size reduction but no statistical significant difference due to the small simple size.

Keywords: Antera3D camera, Benzoyl peroxide (BP), Facial pore size, Niacinamide

APPENDIX B
ACCEPTANCE LETTER

Acceptance Letter

Date: 29 APRIL 2019

Subject: ICIM 2019 in Bangkok

Dear **Tarnyamas Kaewsanit**

We are pleased to inform you that your paper **"Clinical Comparison Between Topical 2.5%Benzoyl Peroxide + 5% Niacinamide and 2.5%Benzoyl Peroxide in Reducing Facial Pore Size of Patients with Facial Acne Vulgaris"** has been accepted for a session of oral presentation at the 1st International Conference on Integrative Medicine for Wellness (ICIM2019) on June 6-7, 2019 in Bangkok. The conference is organized by Dhurakij Pundit University (DPU).

Attachment is the reviewer's feedback of your paper. Please kindly submit a revised full paper to us before May 10, 2019 so that your paper will be published in our conference proceedings. For a format of a full paper, please follow the instruction on the website (www.dpu.ac.th/icimw2019).

We would appreciate if you could please make a registration payment to our university account as detail attached, and kindly send us a bank slip to www.dpu.ac.th/icimw2019 before May 10, 2019.

Account Name: DHURAKIJ PUNDIT UNIVERSITY
Account Number: 6472001114
Bank name: KASIKORNBANK
Branch: URBANSQUARE(PRACHACHUEN12)

Please be informed that your paper remains on stand-by status until ALL the above requirements are completed.

Should you require any information, please do not hesitate to contact us via this email address.

We look forward to welcoming you to the ICIM2019 at DPU in Bangkok.

Sincerely,

Dr.Banchob Junhasavasdikul,M.D.
Editor-in-chief – ICIM2019

APPENDIX C
ETHIC APPROVAL

หนังสือรับรองการพิจารณาด้านจริยธรรมการวิจัยในคน
คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์)

95 หมู่ 8 ถ.พหลโยธิน ต.คลองหนึ่ง อ.คลองหลวง จ. ปทุมธานี 12120
โทร. 02-9269704 , โทรสาร 02-5644444 ต่อ 7535

.....

หนังสือรับรองเลขที่ 194/2561

โครงการวิจัยเรื่อง การศึกษาเปรียบเทียบระหว่างผลของยาทา 5% ไนอะซินาไมด์ ร่วมกับ 2.5% เบนโซอิลเปอร์ออกไซด์ กับ 2.5% เบนโซอิลเปอร์ออกไซด์ในภาวะสิวรุนแรงน้อยถึงปานกลาง

รหัสโครงการวิจัย MTU-EC-OO-2-107/61

ผู้วิจัย พญ.ธาญมาส แก้วสนิท
ผศ.นพ.พัลลภ จักรวิทย์ธำรง

หน่วยงานที่รับผิดชอบ วิทยาลัยแพทยศาสตร์นานาชาติจุฬาภรณ์ มหาวิทยาลัยธรรมศาสตร์
โทร. 089-7335611

เอกสารที่รับรอง

1. โครงร่างการวิจัย ฉบับปรับปรุงแก้ไขครั้งที่ 3 วันที่ 20 กันยายน 2561
2. เอกสารชี้แจงข้อมูลสำหรับอาสาสมัคร ฉบับปรับปรุงแก้ไขครั้งที่ 3 วันที่ 20 กันยายน 2561
3. เอกสารแสดงความยินยอมเข้าร่วมโครงการวิจัย เวอร์ชั่น 2 วันที่ 16 กรกฎาคม 2561
4. แบบสอบถาม วันที่ 20 กันยายน 2561

คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์) พิจารณาจริยธรรมการวิจัยโดยยึดหลักของ Declaration of Helsinki, The Belmont Report, CIOMS Guidelines และ the International Practice (ICH-GCP)

คณะอนุกรรมการจริยธรรมการวิจัยในคน มหาวิทยาลัยธรรมศาสตร์ ชุดที่ 1 (คณะแพทยศาสตร์) ได้พิจารณาอนุมัติด้านจริยธรรมการทำวิจัยในคนให้ดำเนินการวิจัยข้างต้นได้ ตามมติที่ประชุมครั้งที่ 11/2561 วันที่ 12 มิถุนายน 2561

ระยะเวลาที่อนุมัติ 1 ปี

กำหนดส่งรายงานความก้าวหน้า 1 ปี : วันที่ 1 ตุลาคม 2562

ลงชื่อ.....
(รองศาสตราจารย์ นายแพทย์ไวพจน์ จันทร์วิเมลือง)
ประธานคณะอนุกรรมการฯ

ลงชื่อ.....
(ผู้ช่วยศาสตราจารย์ ดร.สุมาลี คอนโด)
อนุกรรมการและผู้ช่วยเลขานุการ

อนุมัติ ณ วันที่ 2 ตุลาคม 2561
หมดอายุ วันที่ 1 ตุลาคม 2562

APPENDIX D
CASE RECORD FORM

วันที่	**แบบฟอร์มบันทึกข้อมูล** (Case Record Form)

Subject identification NO ☐☐

Part A: ประวัติผู้ป่วย

1. **สัญชาติ** ☐ 1.ไทย ☐ 2.คอเคเซียน ☐ 3.เอเชีย ชาติอื่นๆ..... ☐ 4.อื่นๆ .....

2.**เพศ** ☐ 1.ชาย ☐ 2.หญิง **3.วัน เดือน ปีเกิด** (วันที่/เดือน/ปีพ.ศ.) ☐☐☐

4.**โรคประจำตัว** ☐ 1.ไม่มี ☐ 2.มี ระบุ.....

5.**ยาที่ใช้ประจำ** ☐ 1.ไม่มี ☐ 2.มี ระบุ .....

Part B: ตรวจร่างกายโดยแพทย์

6. lesion counts

comedones		Inflammatory lesions	
Right side	Left side	Right side	Left side

10. acne grade (by The Leeds revised acne grading system).....

11. melanin index by Antera® 3D camera: Right side .....Left side .....

12. Hb index by Antera® 3D camera : Right side .....Left side .....

13. sebum casual level by sebumeter® : Right side .....Left side .....

Part C : เกณฑ์แยกอาสาสมัครออกโดยแพทย์

1. ได้รับยาปฏิชีวนะ, ยาสเตียรอยด์, ยาเม็ดคุมกำเนิด, ยา finasteride แบบรับประทานภายใน 1 เดือนก่อนเข้าร่วมวิจัย ☐ มี ☐ ไม่มี
2. ใช้ยาทารักษาสิวภายใน 2 สัปดาห์ ก่อนเข้าร่วมวิจัย ☐ มี ☐ ไม่มี
3. รับประทานยากลุ่ม retinoids 1 ปีก่อนเข้าร่วมวิจัย ☐ มี ☐ ไม่มี
4. ได้รับยาคุมกำเนิด, ฮอร์โมน estrogen, สเตียรอยด์ แบบฉีดเข้ากล้ามภายใน 3 เดือนก่อนเข้าร่วมวิจัย ☐ มี ☐ ไม่มี
5. โรคประจำตัว ได้แก่ โรคทางระบบต่อมไร้ท่อม โรคตับ แผลในกระเพาะและลำไส้ หรือมีประวัติแผลในกระเพาะหรือลำไส้ หรือโรคเก๊าท์ ☐ มี ☐ ไม่มี
6. ทำdermabrasion หรือ laser resurfacing ภายใน 2 เดือนก่อนเข้าร่วมวิจัย ☐ มี ☐ ไม่มี
7. ใช้สบู่ทางการแพทย์, ครีมเครื่องสำอางสำหรับลดสิว ภายใน 7 วันก่อนเข้าร่วมวิจัย ☐ มี ☐ ไม่มี
8. ตั้งครรภ์หรือให้นมบุตร ☐ มี ☐ ไม่มี
9. ประวัติแพ้ยาทาชนิด benzoyl peroxide หรือ ยาทาหรือครีมที่มีส่วนประกอบของNiacinamide ☐ มี ☐ ไม่มี
10. สูบบุหรี่ ☐ มี จำนวน.....มวน เป็นเวลา .....ปี ☐ ไม่มี
11. ดื่มสุรา ☐ มี จำนวน .....แก้ว จำนวน .....ครั้ง ภายใน 1 เดือนที่ผ่านมา ☐ ไม่มี
12. เข้ารับการผ่าตัดใหญ่ ภายใน 3 เดือนก่อนเข้าร่วมวิจัย ☐ มี ☐ ไม่มี

Part D : เกณฑ์คัดเข้าโดยแพทย์

1. ผู้ป่วยอายุระหว่าง 18-40 ปี ☐ ใช่ ☐ ไม่ใช่
2. อ่านและยินยอมลงนามในแบบฟอร์ม inform consent ☐ ใช่ ☐ ไม่ใช่
3. สิวความรุนแรงเล็กน้อยถึงปานกลาง (จาก The Leeds revised acne grading system) ☐ ใช่ ☐ ไม่ใช่

ข้ายืนยันว่าข้อมูลที่กรอกมีความถูกต้อง และสมบูรณ์

ผู้ลงข้อมูล ..... รหัส ☐☐☐ วันที่ ☐☐/☐☐/2 5☐☐

แพทย์ผู้ตรวจสอบ ..... รหัส ☐☐☐ วันที่ ☐☐/☐☐/2 5☐☐

dd mm yyyy (พ.ศ.)

Version update วันที่ 20 กันยายน 2561

วันที่

แบบฟอร์มบันทึกข้อมูล (Case Record Form)

Subject identification NO ☐☐ สัปดาห์ที่ ☐☐

Part A: การตรวจร่างกายโดยแพทย์

1. lesion counts

comedones		Inflammatory lesions	
Right side	Left side	Right side	Left side

2. acne grade (by The Leeds revised acne grading system).....
3. melanin index by Antera® 3D camera: Right side .....Left side .....
4. Hb index by Antera® 3D camera : Right side .....Left side .....
5. sebum casual level by sebumeter® : Right side .....Left side .....

Part B: การประเมินความเปลี่ยนแปลงและผลข้างเคียงโดยแพทย์ และผู้เข้าร่วมวิจัย

ใบหน้าข้างขวา

1. ความเปลี่ยนแปลงของจำนวนสิว (โดย แพทย์)
   a. ไม่เปลี่ยนแปลง(0%)
   b. เปลี่ยนแปลงเล็กน้อย (0-25%)
   c. เปลี่ยนแปลงปานกลาง (26-50%)
   d. เปลี่ยนแปลงอย่างมาก (51-75%)
   e. เปลี่ยนแปลงอย่างยิ่ง (76-100%)
2. คะแนนความพอใจ (โดย ผู้เข้าร่วมวิจัย)
   a. ไม่เปลี่ยนแปลง(0%)
   b. เปลี่ยนแปลงเล็กน้อย (0-25%)
   c. เปลี่ยนแปลงปานกลาง (26-50%)
   d. เปลี่ยนแปลงอย่างมาก (51-75%)
   e. เปลี่ยนแปลงอย่างยิ่ง (76-100%)
3. การประเมินผลข้างเคียง(โดย ผู้เข้าร่วมวิจัย)

อาการคัน	มี ☐	ไม่มี ☐
อาการแสบร้อน	มี ☐	ไม่มี ☐
สะเก็ด	มี ☐	ไม่มี ☐
ความมัน	มี ☐	ไม่มี ☐
ผิวหนังอักเสบ	มี ☐	ไม่มี ☐

ใบหน้าข้างซ้าย

1. ความเปลี่ยนแปลงของจำนวนสิว (โดย แพทย์)
   a. ไม่เปลี่ยนแปลง(0%)
   b. เปลี่ยนแปลงเล็กน้อย (0-25%)
   c. เปลี่ยนแปลงปานกลาง (26-50%)
   d. เปลี่ยนแปลงอย่างมาก (51-75%)
   e. เปลี่ยนแปลงอย่างยิ่ง (76-100%)
2. คะแนนความพอใจ (โดย ผู้เข้าร่วมวิจัย)
   a. ไม่เปลี่ยนแปลง(0%)
   b. เปลี่ยนแปลงเล็กน้อย (0-25%)
   c. เปลี่ยนแปลงปานกลาง (26-50%)
   d. เปลี่ยนแปลงอย่างมาก (51-75%)
   e. เปลี่ยนแปลงอย่างยิ่ง (76-100%)
3. การประเมินผลข้างเคียง(โดย ผู้เข้าร่วมวิจัย)

อาการคัน	มี ☐	ไม่มี ☐
อาการแสบร้อน	มี ☐	ไม่มี ☐
สะเก็ด	มี ☐	ไม่มี ☐
ความมัน	มี ☐	ไม่มี ☐
ผิวหนังอักเสบ	มี ☐	ไม่มี ☐

ฉันยืนยันว่าข้อมูลที่กรอกมีความถูกต้อง และสมบูรณ์

ผู้ลงข้อมูล ..... รหัส ☐☐☐ วันที่ ☐☐/☐☐/25☐☐ (พ.ศ.)

แพทย์ผู้ตรวจสอบ ..... รหัส ☐☐☐ วันที่ ☐☐/☐☐/25☐☐ dd mm yyyy (พ.ศ.)

Version update วันที่ 20 กันยายน 2561

BIOGRAPHY

Name	Miss Tarnyamas Kaewsanit
Date of Birth	February 3, 1990
Education attainment	Academic Year 2013; Doctor of Medicine, Chulalongkorn university, Thailand Academic Year 2018; Master of Science (Dermatology) Chulabhorn International College of Medicine Thammasat University, Thailand
Work experience	2014; General practice internship, Hatyai hospital, Songkhla, Thailand 2015; General practictioner, Hatyai hospital, Songkhla, Thailand