



**THE PEELING EFFECT OF TOPICAL 15% TRANEXAMIC ACID
IN INFLAMMATORY ACNE TREATMENT**

CHAWALEE CHUEACHAVALIT

**MASTER OF SCIENCE
IN
DERMATOLOGY**

**SCHOOL OF ANTI-AGING AND REGENERATIVE MEDICINE
MAE FAH LUANG UNIVERSITY**

2024

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ABSTRACT

Objective: To evaluate the efficacy of a 15% tranexamic acid (TXA) emulgel in inducing skin peeling, treating acne, and reducing periorbital wrinkles. Additionally, to assess its impact on transepidermal water loss (TEWL), sebum level, stratum corneum integrity, and submental TEWL. Finally, to evaluate the side effects and satisfaction associated with the treatment.

Methods: A randomized, double-blind, placebo-controlled, split-face study was conducted on 15 participants with mild to moderate acne. Participants applied a 15% TXA emulgel to one side of the face and a placebo to the other, twice daily for the first four weeks. For the subsequent four weeks, they switched to applying the placebo on both sides of the face. All parameters were assessed at baseline, and weeks 1, 2, 3, 4, and 8. The collection of the stratum corneum was conducted at baseline and week 4.

Results: The 15% TXA significantly increased the desquamation index starting from week 3 ($p=0.035$) onward, accompanied by a significant elevation in TEWL starting from week 3 ($p=0.013$) and a decrease in sebum level starting from week 2 ($p=0.039$) compared to the placebo group. In terms of stratum corneum quantification,

more layers were collected via the tape-stripping procedure at week 4 (48.35 ± 13.66) on the TXA side compared to the placebo side (44.51 ± 9.47) during the same week, and to its baseline (46.49 ± 15.14). Despite these observations, no significant differences were found between or within the groups. Submental TEWL after stratum corneum removal by the tapes showed a significant difference between baseline and week 4 ($p=0.027$) in the TXA group. In terms of acne treatment, statistically significant differences were observed in both total inflammatory and total non-inflammatory acne lesion counts between the 15% TXA group and the placebo group, commencing from week 2 ($p=0.005$) for the total inflammatory acne and week 3 ($p=0.047$) onward for the total non-inflammatory acne. A significant reduction in erythema of inflammatory papules was noted in the TXA group, evident from week 2 ($p=0.019$), compared to the placebo group. Furthermore, the TXA group exhibited a significant improvement in periorbital fine lines, with a significant reduction in the mean wrinkle score between baseline and week 1 ($p=0.020$). Regarding safety, out of 15 participants, seven subjects experienced mild erythema during weeks 2 through week 4, and five subjects reported mild itching on the TXA-treated sides. These side effects were perceived as minimal and tolerable, resolving spontaneously. Participants expressed satisfaction with the acne treatment and rejuvenation effects attributed to the desquamative properties of the 15% TXA formulation.

Conclusion: The findings suggest that the 15% TXA emulgel is a promising option for acne treatment and skin rejuvenation.

Keywords: Acne Vulgaris, Tranexamic Acid (TXA), Anti-inflammatory Effect, Desquamation, Transepidermal Water Loss (TEWL), Sebum, Protein Assay, Periorbital Wrinkle

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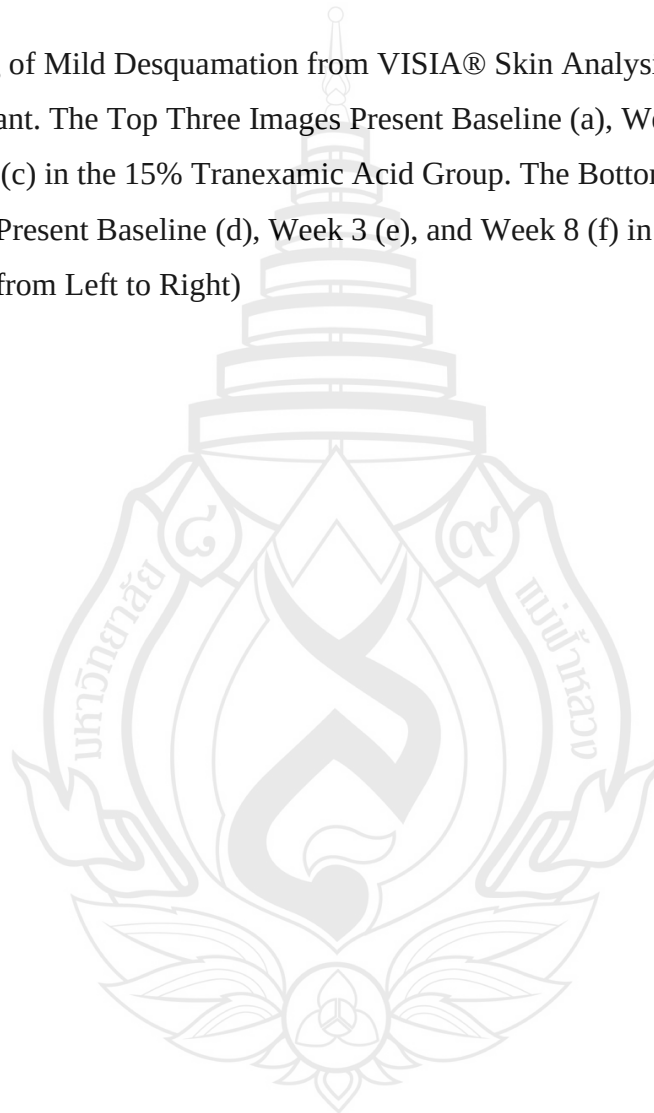
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ABBREVIATIONS AND SYMBOLS

AAD	The American Academy of Dermatology
AD	Atopic dermatitis
AHA	Alpha hydroxy acids
α -MSH	Alpha-melanocyte-stimulating hormone
AMPs	Antimicrobial peptidesVermont
AZA	Azelaic acid
bFGF	Basic fibroblast factor
BHA	Beta hydroxy acids
BMT	Brimonidine tartrate
BP	Benzoyl peroxide
<i>C. acnes</i>	<i>Cutibacterium acnes</i>
CAMP	Christie-Atkins-Munch-Petersen factor
CEA	Clinical erythema assessment
Cm ²	Centimeter square
Cmax	Maximum concentration
CO ₂	Carbon dioxide
COCs	Combined oral contraceptives
CRH	Corticotropin-releasing hormoneWashington
DI	Desquamation index
DHT	Dihydrotestosterone
ENO1	Enolase 1
ETR	Erythematotelangiectatic rosacea
GAIS	Global aesthetic improvement score
GCP	Good Clinical Practice
GM-CSFWI	Granulocyte-macrophage colony-stimulating factor Wisconsin

ABBREVIATIONS AND SYMBOLS (continued)

HaCaT	High sensitivity of human epidermal keratinocytes
HBD-2	Human β -defensin-2
HQ	Hydroquinone
HUVEC	Human umbilical vein endothelial cells
ICAM-1	Intercellular adhesion molecule 1
IGA	Investigator's global assessment
IGARSS	The International Geoscience and Remote Sensing Symposium
IGF-1	Insulin-like growth factor-1
IL	Interleukin
IL-1 α	Interleukin-1 α
Kg	Kilogram
KLK5	Kallikrein-5
L	Liter
M	Molarity
MAPK	Mitogen-activated protein kinase pathway
MASI	The melasma area and severity index score
MelasQoL	Melasma quality of lifescape
MI	Melanin index
min.	Minute
mL	Milliliter
MMPs	Matrix metalloproteinases
OXZ	Oxymetazoline
PAE	Persistent post acne erythema
PAHPI/PAHI	Postacne hyperpigmentation index
PAR-2	Protease-activated receptor 2 receptor
PGA	Physicians global assessment

ABBREVIATIONS AND SYMBOLS (continued)

PIE	Post-inflammatory erythema
PIH	Post-inflammatory hyperpigmentation
PPAR	Peroxisome proliferator-activated receptor pathway
PSA	Patient self-assessment score
%	Percentage
RQoL	Rosacea-specific quality of life score
SC	Stratum corneum
SD	Standard deviation
SLS	Sodium lauryl sulfate
SP	Serine protease
t-AMCHA	(Aminomethyl)cyclohexane carboxylic acid
TCA	Trichloroacetic acid
TEWL	Transepidermal water loss
Th1	T helper cell type 1
TLR2	Toll-like receptor 2
Tmax	Time to peak drug concentration
TNF- α	Tumor necrosis factor-alpha
TS	Tape stripping/Tape strip
TSDf	Topical steroid-dependent/damaged face
TXA/TA	Tranexamic acid
μ	micro-
uPA	Urokinase-type plasminogen activator
VCAM-1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
VWD	von Willebrand disease

CHAPTER 1

INTRODUCTION

1.1 Background

Acne is a chronic inflammatory skin disease that affects the pilosebaceous unit. It commonly occurs on the face, neck, and upper body. The age group most frequently affected by acne is adolescents to middle-aged individuals, accounting for 85% of the global population aged between 12 and 25 years (Kang et al., 2019). Acne can be classified into two main types: comedones and inflammatory acne. Comedones can be further divided into closed comedones (whiteheads) and open comedones (blackheads). Inflammatory acne has various presentations depending on severity, including papules, pustules, nodules, and cysts. The pathogenesis of acne involves an inflammatory process in the normal hair follicles of individuals prone to acne. CD4⁺ T helper cell Type 1 (Th1) memory cells and macrophages infiltrate in the areas of normal hair follicles, and angiogenesis is observed in the nearby regions (Holland & Jeremy, 2005). The next mechanism is the formation of comedones, which occurs due to hyperkeratinization and reduced desquamation of the follicular epithelial cells, leading to obstruction of the hair follicles. Subsequently, there is hyperseborrhea and dysseborrhea, resulting in the accumulation of sebum in the hair follicles. It has been found that 54% of inflammatory acne originates from comedones, and 26% develops from normal skin (Kang et al., 2019). The next stage is the development of acne inflammation, which is caused by dysbiosis of the *Cutibacterium acnes* or *C. acnes* on the skin, leading to an increase in the virulent strain types. *C. acnes* secrete lipases, proteases, and hyaluronate lyase, which stimulate the innate immune system and trigger the inflammatory process of acne. The final mechanism of inflammatory acne is inflammation. This involves the activation of Toll-like receptor 2 (TLR2) and Protease-activated receptor 2 (PAR-2) on the surface of monocytes, sebocytes, and keratinocytes by *C. acne* and Insulin-like growth factor-1 (IGF-1), resulting in the secretion of pro-inflammatory mediators (Cong et al., 2019).

The assessment of acne severity and treatment can be performed based on the evaluation of acne lesion characteristics and count. In this research study, The Evaluator's Global Acne and Severity Scale (Callender et al., 2012) is employed for acne assessment. Regarding acne treatment, the American Academy of Dermatology (AAD) 2016 guidelines (Reynolds et al., 2024) recommend that mild acne should be primarily managed with topical therapies, including topical retinoids, benzoyl peroxide (BP), and antibiotics as the first-line treatment options. For moderate to severe acne, systemic medications such as oral antibiotics, hormonal agents, or isotretinoin should be considered in addition to topical treatments to achieve optimal therapeutic outcomes.

Since acne is a chronic inflammatory skin disease, despite the availability of various treatment modalities, individual responses to treatment vary considerably. Therefore, additional research is being conducted to discover new medications to enhance acne treatment, similar to the study by (Charoenwattanayothin et al., 2022), which found that tranexamic acid (TXA), used in the treatment of melasma, can effectively treat inflammatory acne at a concentration of 10% after 4 weeks of treatment. However, a side effect of mild stratum corneum peeling was observed in 11% of the study participants. This observation led to the hypothesis that TXA may also possess properties that promote stratum corneum exfoliation.

Tranexamic acid or transamin is a synthetic derivative of the amino acid lysine, with the chemical name trans-4-aminomethyl-cyclohexanecarboxylic acid ($C_8H_{15}NO_2$). TXA has several properties, including (I.) Hemostatic properties in individuals with blood clotting disorders, (II.) Reduction of hyperpigmentation caused by melasma (III.) Reduction of erythema caused by inflammation in rosacea (IV.) Recently discovered ability to reduce inflammatory acne. The main mechanism of action of TXA is the inhibition of the conversion of plasminogen to plasmin in various body organs. If this process occurs in the blood and vascular system, TXA inhibits the dissolution of blood clots that occlude injured or ruptured blood vessels resulting from trauma or surgery by preventing plasmin from degrading fibrin (Åstedt, 1987; Syrovets et al., 2012). In the treatment of melasma, TXA reduces the melanin production process in melanocytes by inhibiting the formation of plasmin, which stimulates melanin synthesis (Maeda, 2022). In the treatment of inflammatory acne, post-inflammatory erythema (PIE) acne, post-inflammatory hyperpigmentation (PIH) acne, and rosacea, TXA inhibits the plasmin formation on monocytes and macrophages, as well as inhibits the

activation of TLR2 and PAR-2 receptors on keratinocytes and sebocytes, thereby suppressing the secretion of pro-inflammatory mediators (Jakhar & Kaur, 2020; Li et al., 2019; Syrovets et al., 2012; Zhong et al., 2015).

As mentioned above, since stratum corneum peeling is a side effect observed with the use of 10% TXA (Charoenwattanayothin et al., 2022) Given that stratum corneum peeling, a side effect observed with the use of 10% TXA, occurred in only a small group of participants, the researcher is keen on investigating whether increasing the concentration of TXA to 15% would not only enhance its exfoliating efficacy but also maintain its anti-inflammatory effects on acne. If TXA at this concentration indeed impacts the exfoliation of dead skin cells, it could potentially stimulate the renewal of skin cells, reduce signs of aging, and promote a more youthful appearance of the skin, in addition to its ability to treat inflammatory acne.

1.2 Research Question

Did the application of topical 15% TXA cause a greater peeling effect and reduction in the number of mild to moderate facial acne lesions compared to the placebo?

1.3 Objectives

1.3.1 To evaluate the efficacy of 15% TXA emulgel in causing skin peeling compared to a placebo emulgel.

1.3.2 To evaluate the efficacy of 15% TXA emulgel in reducing acne vulgaris compared to a placebo emulgel.

1.3.3 To evaluate the effect of transepidermal water loss (TEWL), sebum level, protein quantification, and submental TEWL on 15% TXA emulgel compared to a placebo emulgel.

1.3.4 To evaluate the efficacy of a 15% TXA emulgel in improving periorbital fine wrinkles compared to a placebo emulgel.

1.3.5 To evaluate the side effects of topical 15% TXA emulgel.

1.3.6 To evaluate subjects' satisfaction after using topical 15% TXA emulgel.

1.4 Scope of Research

The study aimed to evaluate the effects of a topical 15% TXA emulgel formulation on various skin parameters compared to the placebo. The primary objectives were to assess the peeling or desquamative properties, anti-acne efficacy in reducing facial mild to moderate acne vulgaris lesions, and rejuvenation effect on periorbital wrinkles resulting from the skin peeling action. Additionally, the study sought to investigate the impact on TEWL change, sebum production, stratum corneum integrity, and submental TEWL change. The study employed a split-face, double-blind, randomized, placebo-controlled design. Participants applied the active emulgel twice daily for an initial 4-week period, followed by a subsequent 4-week period using a placebo emulgel, culminating in an 8-week total duration, while the placebo emulgel was applied for the entire 8-week duration. Comprehensive assessments were conducted at baseline, weeks 1, 2, 3, 4, and 8, to monitor changes in the aforementioned skin parameters attributed to the TXA intervention relative to placebo. Furthermore, adverse events and participant-reported satisfaction were documented throughout the study period. The study population comprised volunteers aged 18 to 25 years. The clinical trial was executed at Mae Fah Luang University Hospital in Bangkok over four months, with complementary laboratory analyses performed at Mahidol University, Faculty of Public Health, Department of Microbiology for a few months.

1.5 Conceptual Framework

1.5.1 Conceptual Framework of Peeling Mechanism

The mechanism behind the peeling effect caused by TXA is not well understood. However, it is presumed that topical TXA weakens the intercellular cohesion force, leading to skin desquamation. Two concepts involve skin peeling induced by chemical agents. The first is a chemical peel used for skin rejuvenation, and the other is keratolysis, used in acne treatment.

Chemical peeling agents work through three main mechanisms: metabolic, causative, and toxic (Prendergast & Shiffman, 2011) Alpha-hydroxy acids (AHA) and beta-hydroxy

acids (BHA) act through metabolic action. Trichloroacetic acid (TCA) acts through causative action. Finally, Phenol and resorcinol act through toxic action.

Keratolysis involves various modes of action in different keratolytic agents. For example, oxidation reaction, reduction reaction, genetic regulation and inhibition of gene expression, inter-corneocyte cohesion disruption and dissolution of intercellular cement, reduction of filaggrin production, and inhibition of the ionic bond-forming enzyme, as demonstrated in Figure 1.1.

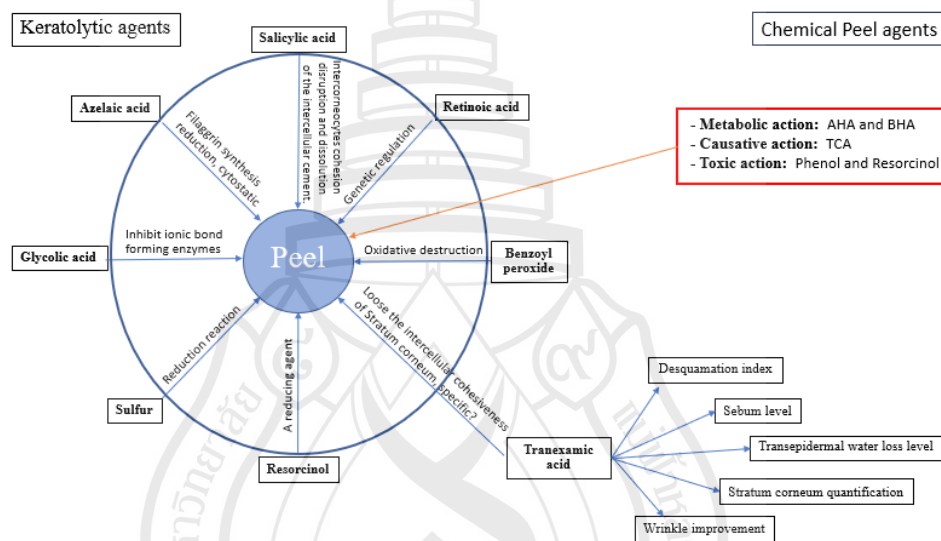


Figure 1.1 Conceptual Framework of Peeling Mechanism

1.5.2 Conceptual Framework of Inflammatory Acne

TXA represses the activity of TLR-2 and PAR-2 pathways, which are induced by the virulent strain types of *C. acnes* in monocytes/macrophages and keratinocytes. Thus reducing the production of the proinflammatory cytokines. See Figures 1.2(a) and 1.2(b).

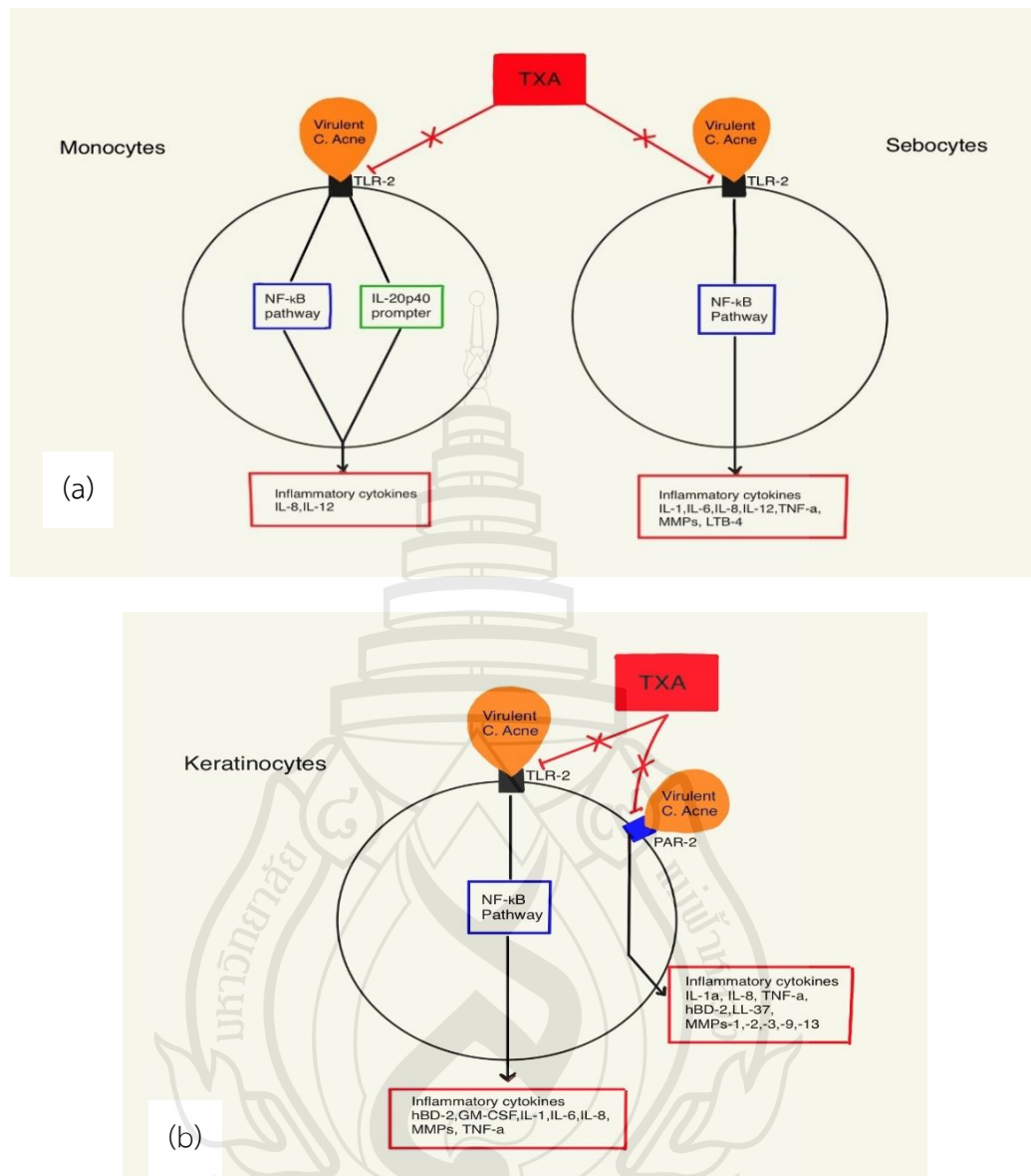


Figure 1.2 Conceptual Framework of Inflammatory Acne

1.6 Operation Definitions

1.6.1 Acne vulgaris is a common chronic inflammatory skin disorder affecting the pilosebaceous unit, which includes the hair follicle, hair shaft, and sebaceous gland. Various factors contribute to the differences in acne formation and severity.

1.6.2 The efficacy of the treatment for inflammatory acne was assessed by evaluating acne lesion counts, acne severity grades, and the degree of improvement in acne erythema at weeks 1, 2, 3, 4, and 8, compared to baseline measurements.

1.6.3 Acne lesion count is a method used to evaluate acne severity by counting all types of acne lesions (non-inflammatory and inflammatory acne).

1.6.4 Acne severity grading was assessed using the Evaluator's Global Acne and Severity Scale, which was divided into clear, almost clear, mild, moderate, severe, and very severe.

1.6.5 The degree of improvement in acne erythema was evaluated by grading it four points, which were divided into clear, light pink, dull red, and dark red.

1.6.6 Keratolysis is the losing or shedding of the stratum corneum layer of the skin. The keratolytic mechanism is to disintegrate desmosomes and hemidesmosomes that connect keratinocytes and bind to the surrounding extracellular matrix (Alikhan & Maibach, 2014; Hatakeyama et al., 2004).

1.6.7 Efficacy of inducing desquamation formation was measured by desquamation index, sebum level, and TEWL level at weeks 1, 2, 3, 4, and 8 compared to baseline. Stratum corneum was collected via tape stripping technique, and submental TEWL was performed at week 4 compared to the baseline.

1.6.8 Facial desquamation was assessed by physical examination and photo evaluation. The desquamation index was documented compared to the baseline. The higher the desquamation index, the greater the chance that desquamation will occur as the skin becomes drier. On the other hand, the lower the desquamation index, the lesser the chance of desquamation occurring as the skin becomes less dry. However, there is no grading for mild, moderate, and severe degrees of desquamation.

1.6.9 SM-Sebumeter® SM815 measured sebum levels to determine the grease spot through the photometric method to measure sebum secretion on the skin. A high sebum level indicates increased sebum production, while a low level signifies reduced sebum production.

1.6.10 TM-Tewameter® TM300 measured TEWL levels to determine the density gradient of water evaporation from the skin and characterize the skin barrier function. A high level of TEWL signifies unhealthy skin due to impairment of skin barrier function, whereas a low level signifies healthy skin.

1.6.11 A protein assay measures the amount of protein embedded in the removed stratum corneum by the stripping tapes. The procedure involves a series of chemical interactions with the protein molecules. The protein is dyed with a color reagent and undergoes light absorbance measurement by a spectrophotometer.

1.6.12 the periorbital wrinkle was measured with VISIA® Skin analysis in weeks 1, 2, 3, 4, and 8 to see the changes.

1.6.13 Side effects were evaluated at weeks 1, 2, 3, 4, and 8 by history taking and physical examination upon visits, as well as from a questionnaire completed by the subjects.

1.6.14 Satisfaction evaluation was in the form of a questionnaire to assess satisfaction regarding acne reduction, formation of the facial fine scales, and reduction of the periorbital fine lines at weeks 1, 2, 3, 4, and 8. The subjects' satisfaction with product properties was evaluated in week 8.

1.6.15 Tranexamic acid (TXA, trans-4-aminomethylcyclohexanecarboxylic acid), is a synthetic derivative of the amino acid lysine. TXA exhibits an antifibrinolytic property by inhibiting plasmin formation from plasminogen conversion. Thus, prevent fibrin degradation (Gaćina & Ćosić, 2023).

1.6.16 15% TXA emulgel. The composition included ammonium acryloyldimethyltaurate/VP copolymer, glycerine, DI water, disodium EDTA, TXA, caprylic/capric triglyceride, phenoxyethanol, chlorphenesin, and glycerin. The emulgel is white in color with turbidity, pH 7.47. The product came in a plastic bottle size of 15 grams. Coursemetic Lab Co., Ltd, manufactured the product. Placebo emulgel was composed of.

1.6.17 Placebo emulgel. The composition included ammonium acryloyldimethyltaurate/VP copolymer, glycerine, DI water, disodium EDTA, caprylic/capric triglyceride, phenoxyethanol, chlorphenesin, and glycerin. The emulgel is white in color. The product was manufactured by Coursemetic Lab Co., Ltd. It was packaged in a 15-gram plastic bottle.

CHAPTER 2

LITERATURE REVIEW

2.1 Acne Vulgaris

Acne vulgaris is a prevalent chronic inflammatory dermatological condition that affects the pilosebaceous unit, which is comprised of the hair follicle, hair shaft, and sebaceous gland. The manifestation and severity of acne vulgaris are influenced by multifarious factors. This condition is highly prevalent among adolescents and young adults, with an estimated 85% of individuals between the ages of 12 and 25 years being affected (Kang et al., 2019). Persistent acne scarring can have a detrimental impact on an individual's psychological well-being.

2.1.1 The Pathogenesis of Acne

The pathogenesis of acne vulgaris involves four primary mechanisms:

1. Hyperproliferative aberrations in the follicular epidermal lining
2. Excessive sebum secretion coupled with alterations to its biochemical composition
3. Dysbiosis and overgrowth of the cutaneous commensal *Cutibacterium acnes* (*C. acnes*)
4. Induction of inflammatory processes and activation of the immune response

According to Holland and Jeremy's (2005) postulation, the inflammatory processes underlying acne vulgaris represent a preclinical phenomenon that precedes the onset of comedogenic or inflammatory lesions. Their research demonstrated that in clinically normal skin, a substantial population of inflammatory cells, including CD4⁺ helper T lymphocytes and macrophages, exhibit perifollicular infiltration. Furthermore, they observed elevated expression levels of the α v integrin in the dermal vasculature surrounding the follicular units, a molecular signature associated with the initiation of angiogenesis.

Concomitantly, this phenomenon was accompanied by an upregulation of vascular adhesion molecules, namely vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and intercellular adhesion molecule 1 (ICAM-1), which facilitate the recruitment and migration of inflammatory cells into the dermal compartment. The initiation of pre-clinical inflammatory events precipitates the subsequent pathogenesis of acne, as demonstrated in Figure 2.1.

The Four Mechanisms of Acne Pathogenesis.

1. Hyperproliferative Aberrations in the Follicular Epidermal Lining

This pathogenic cascade is characterized by hyperproliferative aberrations in the follicular keratinocytes, concomitant with augmented keratinocyte adhesion in the upper hair follicle and infundibular epithelium, culminating in follicular ostium obstruction. Such an obstructive event precipitates follicular distension due to the accumulation of keratin, sebum, and the commensal bacterium *Cutibacterium acnes* (*C. acnes*), thereby facilitating the formation of microcomedones. The key factors that initiate and propagate this process include the formation of dihydrotestosterone (DHT) and consequent androgenic stimulation of follicular keratinocytes, diminished levels of the essential fatty acid linoleic acid, elevated interleukin-1 α (IL-1 α) cytokine signaling, and the metabolic activities of *C. acnes*.

2. Excessive Sebum Secretion Coupled with Alterations to Its Biochemical Composition

The sebocytes residing within sebaceous glands undergo proliferative and differentiation programs stimulated by various factors, culminating in elevated lipid biosynthesis. The activity and functional regulation of sebocytes is governed by an array of signals, including androgenic stimuli, the insulin/IGF-1 signaling cascade, corticotropin-releasing hormone (CRH), alpha-melanocyte-stimulating hormone (α -MSH), and the neuropeptide substance P (Cong et al., 2019). Alterations in the biochemical profile of sebum are characterized by a diminished ratio of saturated (C16:0) to monounsaturated (C16:1) lipid species, coupled with an augmented linoleic acid content (Yoon et al., 2013). The unsaturated fatty acids oleic acid and linoleic acid exert pivotal regulatory roles in modulating the inflammatory response, achieved through their influence on monocyte differentiation and cytokine secretory profiles. Furthermore, adipokine leptin has been implicated as a key mediator initiating sebocyte inflammatory cascades (Töröcsik et al., 2014). Lipoperoxidation products contribute to the propagation of inflammatory processes via the induction of pro-

inflammatory cytokine signaling and simultaneously stimulate increased sebum production through the peroxisome proliferator-activated receptor (PPAR) pathway. Moreover, the commensal bacterium *Cutibacterium acnes* (*C. acnes*) potentiates the inflammatory milieu by catalyzing the lipolytic breakdown of triglycerides into pro-inflammatory free fatty acid species.

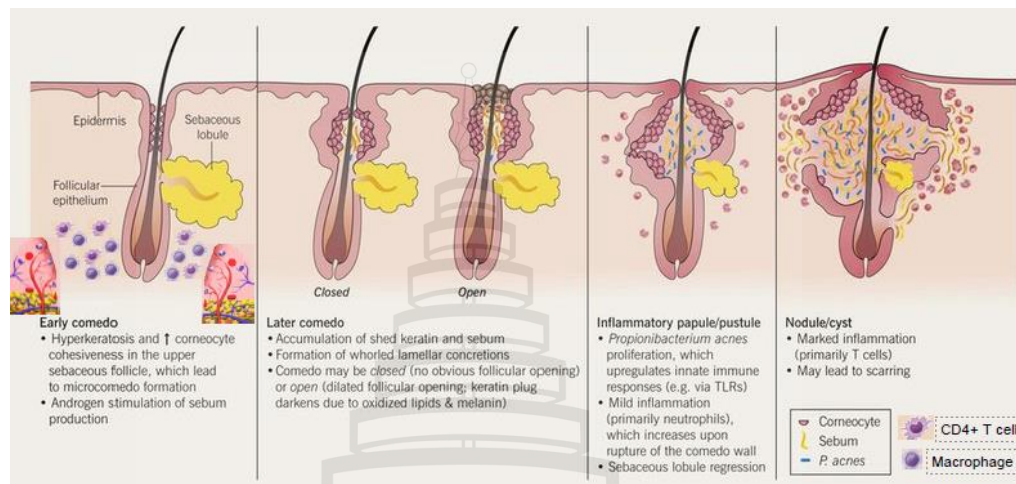
3. Dysbiosis and Overgrowth of the Cutaneous Commensal *Cutibacterium acnes* (*C. acnes*)

Cutibacterium acnes (*C. acnes*) represents a commensal bacterial species prevalent within the human pilosebaceous unit. However, perturbations in the compositional diversity of this microbiota, favoring an expansion of virulent *C. acnes* phylotypes, have been implicated as a precipitating event in the pathogenesis of acne vulgaris lesions. These virulent *C. acnes* strains secrete an array of exoenzymes and metabolites, including lipases, proteases, hyaluronate lyases, endoglycoceramidases, neuraminidases, Christie-Atkins-Munch-Petersen (CAMP) factors, and low-molecular-weight chemotactic peptides (Cong et al., 2019). The combined activities of these bacterial factors potentiate inflammatory processes and facilitate the degradation of host tissues.

4. Induction of Inflammatory Processes and Activation of the Immune Response

The inflammatory processes underlying acne vulgaris pathogenesis involve diverse cellular constituents. Within the sebocytes, exposure to *C. acnes* or IGF-1 triggers the release of an array of pro-inflammatory mediators, including interleukin (IL)-1 β , IL-6, IL-8, IL-12, tumor necrosis factor-alpha (TNF- α), leukotriene B4 (LTB-4), and matrix metalloproteinases (MMPs). The secretion of these cytokines by sebocytes facilitates the recruitment of inflammatory cells into the pilosebaceous unit (Hobbs et al., 1993). In keratinocytes, *C. acnes* induces the activation of Toll-like receptor (TLR)-2 and TLR-4, triggering downstream signaling cascades involving the NF- κ B pathway and mitogen-activated protein kinase (MAPK) pathway, culminating in the release of IL-1, IL-6, IL-8, TNF- α , MMPs, human β -defensin-2 (hBD-2), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Graham et al., 2004; Jugeau et al., 2005; Nagy et al., 2005). Furthermore, *C. acnes* elicits the secretion of IL-1 α , IL-8, TNF- α , hBD-2, LL-37, antimicrobial peptides (AMPs), and MMPs-1, -2, -3, -9, -13 through activation of the protease-activated receptor-2 (PAR-2) (Lee et al., 2010). In the context of the innate immune response, *C. acnes* stimulates monocytes/macrophages via TLR-2, inducing the release of

IL-8 and IL-12 through signaling cascades involving the NF- κ B pathway or the IL-12p40 promoter pathway (Kim et al., 2002). All the acne pathogenesis mechanisms are illustrated in Figure 2.1.



Source Modified from Bologna et al. (2018)

Figure 2.1 Acne Pathogenesis

2.1.2 Types of Acne

Acne vulgaris exhibits a heterogeneous clinical presentation, manifesting in diverse morphological variants. These lesional phenotypes can be categorized into two classes: non-inflammatory and inflammatory acne subtypes, as depicted in Figure 2.2.

2.1.2.1 Non-Inflammatory Acne Lesions:

1. Closed Comedones: Smooth, skin-toned, or whitish papular lesions with a diameter less than 5 mm and a dome-shaped morphology.

2. Open Comedones: Papular lesions characterized by a dilated follicular ostium at the center, with a diameter less than 5mm, containing keratotic plug material.

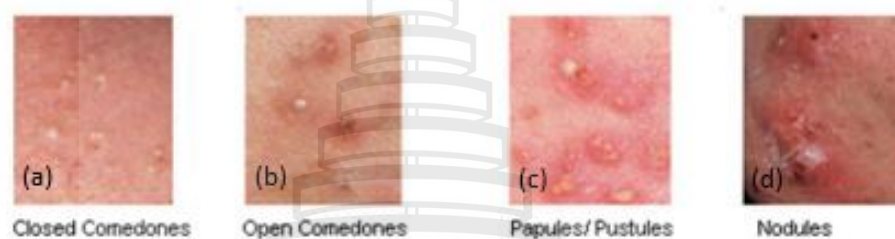
2.1.2.2 Inflammatory Acne Lesions:

1. Papular Acne: Relatively superficial papular eruptions with a diameter of less than 5mm.

2. Pustular Acne: Relatively superficial pustular lesions with a diameter of less than 5mm.

3. Nodular Acne: Deeply seated, tender nodular lesions, categorized as either large papules with a diameter greater than 0.5 mm or nodules with a diameter exceeding 1 cm.

4. Cystic Acne: Deeply situated cystic lesions containing purulent and serosanguinous fluid.



Note (a) Closed Comedones, (b) Open Comedones, (c) Inflamed Papules/Pustules, and (d) Nodular Acne

Source Fernandes and Statham (2011)

Figure 2.2 Different Types of Acne

2.1.3 Grading Severity of Acne

2.1.3.1 The Evaluator's Global Acne and Severity Scale.

Table 2.1 The Evaluator's Global Acne and Severity Scale

Grade	Value	Definition
Clear	0	Normal, clear skin with no evidence of acne vulgaris
Almost clear	1	Rare noninflammatory lesion present, with rare noninflammatory papules (papules must be resolving and may be hyperpigmented, though not pink-red)

Table 2.1 (continued)

Grade	Value	Definition
Mild	2	Som noninflammatory lesion are present, with few inflammatory lesion (papules/pustules only; no nodulocystic lesions)
Moderate	3	Noninflammatory lesion predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules; there may or may not be one small nodulocystic lesion
Severe	4	Inflammatory lesions are more apparent, many comedones, and papules/pustules, there may of may not be a few nodulocystic lesions
Very severe	5	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules, and many nodulocystic lesions

Source Callender et al. (2012)

The Evaluator's Global Acne Severity Scale

Grade 0 (Clear): Normal, clear skin with no evidence of acne vulgaris.

Grade 1 (Almost clear): Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red).

Grade 2 (Mild): Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulocystic lesions).

Grade 3 (Moderate): Non-inflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules; there may or may not be one small nodulocystic lesion.

Grade 4 (Severe): Inflammatory lesions are more apparent, with many comedones and papules/pustules; there may or may not be a few nodulocystic lesions.

Grade 5 (Very severe): Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules, and many nodulocystic lesions.

2.1.3.2 Clinician Erythema Assessment Scales

Table 2.2 Erythema Assessment Scale

Grade	The 4-Point Grading of Acne Erythema	
	Level of disease	Characteristics
0	Non	Clear
1	Mild	Faintly detectable erythema, light pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red

Source Ibrahim et al. (2021)

A 4-Point Grading System for Acne Erythema

Grade 0: Non - The skin appears clear without any erythema.

Grade 1: Mild - There is faintly detectable erythema, presenting as light pink in color.

Grade 2: Moderate - The erythema is a dull red color and is clearly distinguishable.

Grade 3: Severe - The erythema is deep or dark red, indicating a more intense inflammation

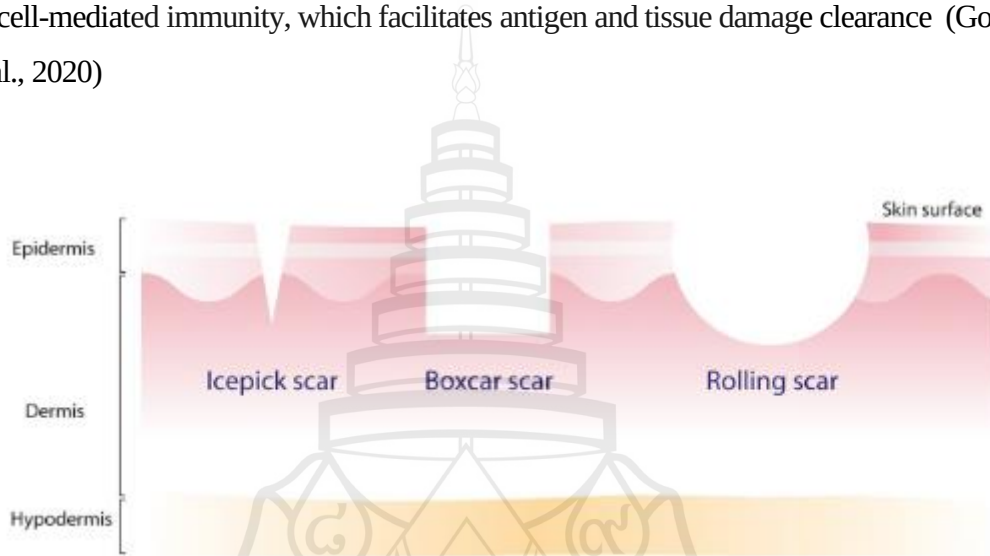
2.1.4 Post-Acne Complications

The prevalent outcomes following the inflammatory phase of acne include post-inflammatory erythema (PIE), post-inflammatory hyperpigmentation (PIH), and acne scars, each characterized by distinct features:

1. Post-inflammatory Erythema (PIE): This condition manifests as dull red or pink lesions that appear post-acne resolution. It is a result of inflammation, dilatation, or damage to the skin's capillaries.

2. Post-inflammatory Hyperpigmentation (PIH): This is evident as increased pigmentation at the sites of healed acne lesions due to excessive melanin production.

3. Acne Scars: These can be classified into atrophic scars (such as ice pick scars, rolling scars, and boxcar scars) and hypertrophic scars (including keloids), shown in Figure 2.3. These scars arise from abnormal healing processes in the pilosebaceous unit, influenced by cell-mediated immunity, which facilitates antigen and tissue damage clearance (Goodarzi et al., 2020)



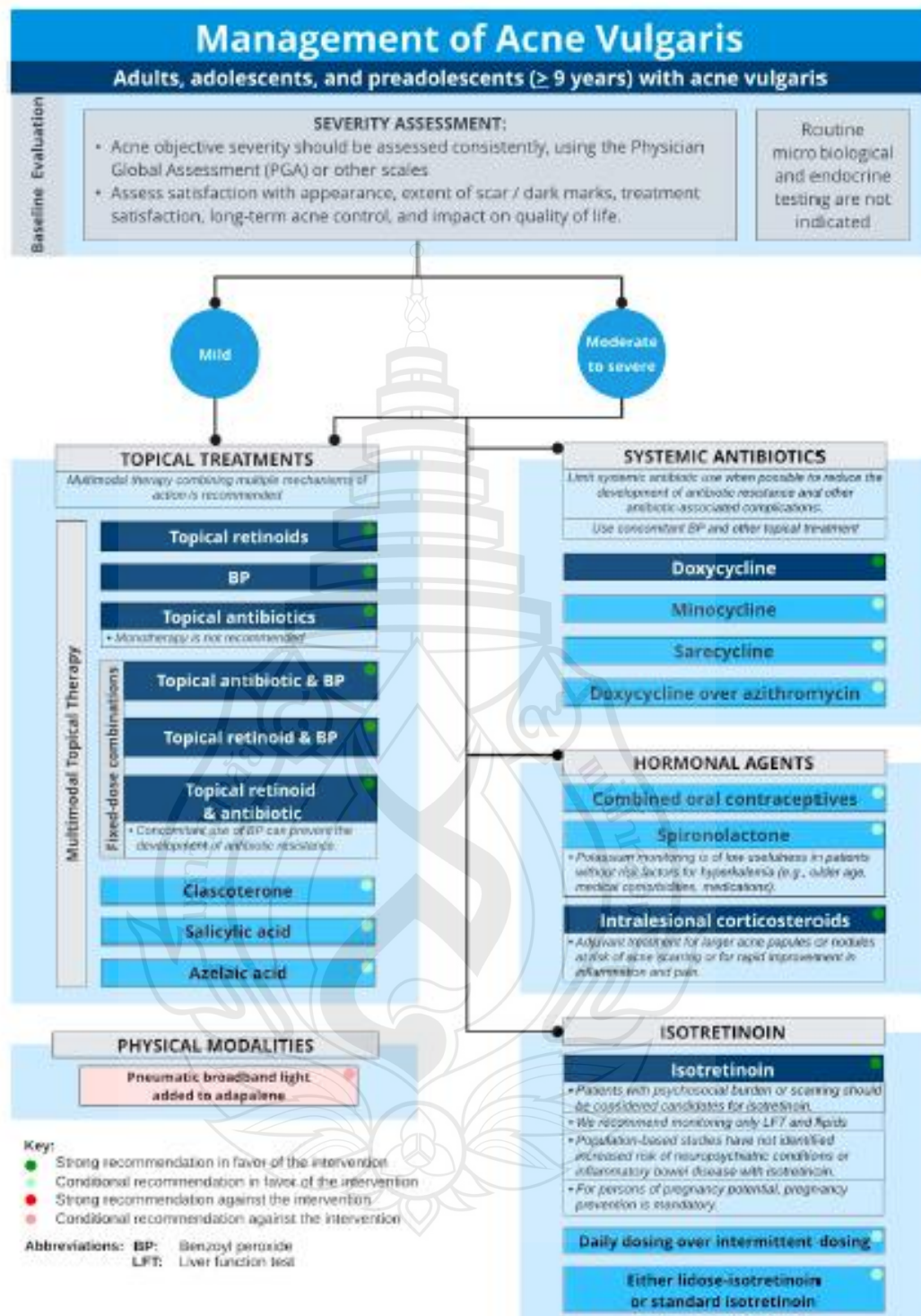
Source Goodarzi et al. (2020)

Figure 2.3 Types of Acne Scars

2.1.5 Acne Treatment

2.1.5.1 Guideline of Acne Treatment

Treatment for acne vulgaris begins with an assessment of the clinical severity of the acne. The approach to treatment is tailored based on the severity of the individual's acne. For cases of mild acne, the American Academy of Dermatology (AAD) 2016 (Reynolds et al., 2024) recommends topical treatments as the initial intervention. In scenarios involving moderate to severe acne, systemic medications in conjunction with topical treatments are advisable, as illustrated in Figure 2.4.



Source Reynolds et al. (2024)

Figure 2.4 Management of Acne Vulgaris

The primary treatment for mild acne consists of topical medications. Topical retinoids, benzoyl peroxide (BP), and antibiotics are highly recommended. Additionally, other topical agents such as clascoterone, salicylic acid, and azelaic acid are conditionally advised depending on the specific circumstances of the acne. These topical medications may be used singly for a monotherapy approach or in fixed-dose combinations, such as those combining retinoids with BP, retinoids with antibiotics, and antibiotics with BP.

In cases of moderate to severe acne, the recommended approach is to use topical medications in conjunction with systemic treatments such as antibiotics, hormonal therapies, or isotretinoin.

2.1.5.2 Medications

1. Topical Medicine

1) Topical Retinoids

Retinoids, derivatives of vitamin A, interact with nuclear RAF receptors to modify gene expression, thereby reducing cell proliferation, differentiation, and inflammation. As a result, they are recognized for their comedolytic and anti-inflammatory properties. The FDA has approved four types of topical retinoids: adapalene, tretinoin, tazarotene, and tazarotene. Common side effects of retinoids include dryness, erythema, a burning sensation, and exfoliation.

2) Benzoyl Peroxide

Benzoyl peroxide (BP) functions as a topical antimicrobial agent and possesses mild comedolytic capabilities. It diminishes bacterial colonization through the release of free oxygen radicals. BP is used in concentrations ranging from 2.5% to 10% for acne treatment. Common side effects of BP include dryness, irritation, a stinging sensation, erythema, and exfoliation.

3) Topical Antibiotics

Topical antibiotics such as erythromycin, clindamycin, dapsone, and minocycline are included in acne treatments. However, the use of topical antibiotics as a standalone treatment is generally discouraged due to concerns about antibiotic resistance. It is commonly advised to use topical antibiotics in conjunction with benzoyl peroxide (BP). Additionally, there have been case reports indicating that topical clindamycin can be associated with *Clostridium difficile*-related colitis and diarrhea (Becker et al., 1981; Parry & Rha, 1986).

4) Clascoterone

Clascoterone is an agent that inhibits the synthesis of androgen-mediated lipids and inflammatory cytokines in sebocytes by blocking the androgen receptor.

5) Salicylic Acid (SA)

Salicylic acid, a lipid-soluble β -hydroxy acid, functions as a comedolytic agent by reducing the cohesion among keratinocytes in the stratum corneum.

6) Azelaic Acid

Azelaic acid, a dicarboxylic acid, possesses both comedolytic and antimicrobial effects. Additionally, it helps correct dyspigmentation, which contributes to a brightening effect on the skin.

2. Systemic Medicine

1) Oral Antibiotics

Oral antibiotics from the tetracycline class, such as doxycycline, sarecycline, and minocycline, inhibit bacterial protein synthesis via the ribosome 30s subunit. In addition to their bacteriostatic properties, these antibiotics also reduce inflammation by downregulating inflammatory cytokines. It is advised to use oral antibiotics in conjunction with benzoyl peroxide (BP).

2) Hormone Agents

Hormonal agents utilized in acne treatment include combined oral contraceptives (COCs) and spironolactone. COCs exhibit anti-androgenic effects by decreasing ovarian production of androgens, reducing circulating free testosterone, elevating levels of sex hormone-binding globulin, and diminishing the activity of 5α -reductase (Reynolds et al., 2024).

3) Spironolactone

Spironolactone acts as an androgen-receptor antagonist and inhibits 5α -reductase activity, reducing testosterone production. Common side effects associated with spironolactone include diuresis, hyperkalemia, breast tenderness, fatigue, and headaches.

4) Isotretinoin

Oral isotretinoin, also known as 13-cis-retinoic acid, is prescribed for the treatment of severe acne, especially in cases resistant to conventional therapies. It is also administered to patients experiencing psychological issues due to acne. Isotretinoin functions

by decreasing the size and secretion of sebaceous glands, reducing sebum production, and preventing the formation of comedones.

3. Other Treatment Options

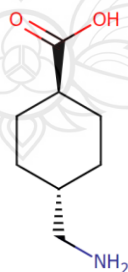
Alternative acne treatments can be used alongside standard therapies. These alternatives include topical chemical peels (AHA and BHA), nicotinamide, and various botanical formulations specifically developed for acne management. Physical treatment modalities also encompass microneedle radiofrequency and photodynamic therapy devices.

2.2 Tranexamic Acid

Tranexamic acid (TXA, trans-4-aminomethylcyclohexanecarboxylic acid) is a synthetic derivative of the amino acid lysine. It demonstrates antifibrinolytic effects by blocking the conversion of plasminogen into plasmin, thereby inhibiting the breakdown of fibrin (Gaćina & Ćosić, 2023). This mode of action prevents the dissolution of blood clots and reduces the risk of severe hemorrhage and other coagulative disorders.

2.2.1 Chemical and Physical Properties

TXA ($C_8H_{15}NO_2$) is characterized as a white, crystalline, odorless powder with a molecular weight of 157.21 g/mol. Its molecular structure is depicted in Figure 2.5. The substance has a melting point exceeding 300 degrees Celsius and is soluble in water (Drugbank Online, 2005).



Source Drugbank Online (2005)

Figure 2.5 Tranexamic Acid Structure

2.2.2 Pharmacology and Biochemistry

The bioavailability of TXA after oral intake ranges from 30% to 50%, and its absorption is unaffected by food consumption. Following multiple oral doses of 1300 mg three times daily over five days, the maximum concentration (C_{max}) reached is 16.41 mcg/mL at a time (T_{max}) of 2.5 hours. The biological half-life in joint fluid is approximately 3 hours, while the half-life for intravenous administration is about 2 hours, with a terminal half-life of around 11 hours (Drugbank Online, 2005).

Initially, the volume of distribution for TXA is 0.18 L/kg, which stabilizes at 0.39 L/kg in a steady state. TXA has the ability to cross the placental barrier, and concentrations in cord blood can match those found in maternal plasma. At therapeutic levels, approximately 3% of TXA is bound to plasma proteins, as it does not attach to serum albumin. The metabolism of TXA is relatively minor, with about 1% of an oral dose excreted as dicarboxylic acid and 0.5% as an acetylated metabolite (Drugbank Online, 2005).

The clearance rate of TXA from plasma is between 110 and 116 mL/min. This agent is predominantly eliminated through the urine by glomerular filtration, with over 95% of the administered dose excreted as the unchanged parent compound. Within 24 hours, 39% of an orally administered dose of TXA is excreted, compared to about 90% of a dose administered intravenously (Drugbank Online, 2005).

2.2.3 Indication of Clinical Use

TXA is prescribed for significant bleeding events and coagulation disorders. It is particularly beneficial for managing hereditary bleeding disorders, including hemophilia, von Willebrand disease (VWD), and hereditary angioedema, where patients may experience excessive bleeding from minor traumas such as nosebleeds, gum bleeding or during dental treatments. Additionally, it is frequently utilized to treat menorrhagia in women with these hereditary conditions (Tengborn et al., 2015).

2.2.4 Contraindication

The overall contraindication of TXA is allergy or hypersensitivity to the agent, ongoing acute venous or arterial thrombosis, medical history or an intrinsic risk of thrombosis or thromboembolism, and who has subarachnoid hemorrhage. Caution must be made when administering TXA to patients with an underlying disease of thromboembolic disease or

hereditary thrombophilia and in patients who take hormonal oral contraceptive medication (Tengborn et al., 2015).

2.2.5 Side Effects and Adverse Effects

- 2.2.5.1 Nausea, vomiting, diarrhea.
- 2.2.5.2 Blood clot problem
- 2.2.5.3 Hemoptysis
- 2.2.5.4 Hemiplegia, slurred speech
- 2.2.5.5 Vision change/loss
- 2.2.5.6 Allergic reaction/anaphylaxis
- 2.2.5.7 Hematuria/oliguria/renal failure
- 2.2.5.8 Orthostatic reaction

In dermatologic treatment with topical TXA, there were minimal reports of side effects, one of which was scaling. However, scaling formation has been observed in some research studies and treatment reports. For example, in a study on the use of 10% TXA gel for treating mild to moderate inflammatory acne, 11% of subjects developed desquamation during week 12 (Charoenwattanayothin et al., 2022). Research by Ebrahimi et al. on the safety and effectiveness of a topical 3% TXA solution versus a combination of 3% hydroquinone and 0.01% dexamethasone for treating melasma identified side effects, including skin irritation, xerosis, and scaling (Ebrahimi & Naeini, 2014).

2.3 Skin Peeling

Currently, the precise mechanism responsible for TXA's peeling effect remains unclear. It is hypothesized that topical application of TXA reduces the force of intercellular cohesion, resulting in skin desquamation.

2.3.1 Chemical Peel

A chemical peel is a procedure where chemical substances are applied to the skin, initiating reactions in the superficial layers. These reactions include keratolysis (the separation of epidermal keratinocytes) and keratocoagulation (the clustering of keratinocytes into a thin surface layer), which are followed by skin exfoliation and renewal of the epidermis.

Subsequently, an inflammatory response promotes the production of fibroblasts, collagen, and glycosaminoglycans, leading to a notable enhancement in skin texture (Conforti et al., 2020). Chemical peels are categorized into three types based on their penetration depth: superficial, medium-depth, and deep peels. Superficial peels affect either all or parts of the epidermis by inducing wounds. Medium-depth peels impact the entire epidermis and may also extend to all or parts of the papillary dermis. Deep peels penetrate the full epidermis and reach down into the reticular dermis, causing extensive wounding.

This paper exclusively examines superficial chemical peeling; therefore, peels of other depths are not discussed. Superficial peels are recommended for conditions such as mild acne and mild forms of melasma affecting the epidermis. Commonly utilized agents in superficial chemical peels include AHAs, such as glycolic acid, mandelic acid, pyruvic acid, lactic acid, and citric acid; BHAs, specifically salicylic acid; Jessner solution; retinoic acid; and trichloroacetic acid (TCA), ranging from 10% to 35 (Lee et al., 2019).

Chemical peeling agents function via three primary mechanisms: metabolic, causative, and toxic, as outlined by Prendergast and Shiffman (2011). AHAs operate metabolically, influencing the functions of enzymes like kinases, sulfotransferases, and phosphotransferases, which impact the sulfate and phosphate content in corneocytes. This activity results in the desquamation of corneocytes, epidermal dryness, and skin shedding. Salicylic acid, a BHA, breaks down the intercellular cement, reducing corneocyte adhesion and displaying keratolytic effects. The causative mechanism is exemplified by TCA, which coagulates proteins in the stratum corneum and leads to corneocyte destruction. The toxic mechanism involves agents such as phenol and resorcinol, which denature proteins, deactivate enzymes, and increase cell membrane permeability, ultimately causing cell death.

2.3.2 Keratolysis

Keratolysis entails the detachment and loosening of the epidermal cell layer from the skin's surface. Agents with keratolytic properties typically function by diminishing the cohesiveness of the stratum corneum. This layer is vital for retaining skin moisture and blocking the entry of deleterious substances. The process involves the breakdown of desmosomes and hemidesmosomes, structures that link keratinocytes together and anchor them to the extracellular matrix (Alikhan & Maibach, 2014; Hatakeyama et al., 2004). Numerous keratolytic agents, primarily utilized for acne treatment, exhibit specific modes of

action that lead to skin desquamation. The mechanisms of keratolytic action are as follows: Oxidative destruction of the corneocytes is found in benzoyl peroxide (BP). The oxidizing surface of lipids and protein is causing vitamin E depletion. As a result, it causes skin dryness and desquamation (Worret & Fluhr, 2006).

Mode of Actions in Keratolytic Agents

1. Decrease keratinocyte adhesion and cohesion molecules is found in topical retinoids. The retinoids deteriorate the stratum corneum skin barrier, reduce follicular keratinocyte coherence, and increase follicular epithelium cell turnover. The mechanism is influenced by genetic regulation and gene expression inhibition (through the downregulation of transcription factors AP-1 and NF-IL60) (Krautheim & Gollnick, 2004).

2. Reduction of filaggrin production. Filaggrin is a crucial element of skin structure, and it maintains the skin barrier. This mechanism is found in azelaic acid.

3. Interorneocyte cohesion disruption and dissolution of intercellular cement is found in salicylic acid.

4. A reducing agent is found in sulfur. Sulfur reacts with cysteine, located in the stratum corneum layer, and generates hydrogen sulfide, which is known to break down keratin.

5. Inhibit ionic bond-forming enzyme, which is essential for the formation of sulfated and phosphorylated mucopolysaccharides, lipid phosphatides, sterol, and glycoproteins. This reduces the electronegative group residing on the outer wall of keratinocytes and corneocytes, diminishing the intercellular cohesion forces. (Van Scott & Ruey, 1984).

6. A reducing agent that interferes with the hydrogen bonds of keratin is found in resorcinol (Monteiro, 2020).

2.4 Wrinkle

Superficial wrinkles arise from textural alterations on the skin's surface, which are attributable to intrinsic aging and photoaging. These wrinkles typically manifest as shallow dermal creases. Treatments for such conditions include chemical peeling, laser resurfacing, and dermabrasion (Lemperle et al., 2001).

2.5 Stratum Corneum Quantification

2.5.1 Tape Stripping

Tape stripping (TS) is a noninvasive technique employed for collecting samples from the epidermis, often serving as an alternative to skin biopsies under specific conditions. The TS method is primarily advantageous for various studies that cover aspects such as skin morphology—including keratinocyte count and barrier function—skin disorders like atopic eczema, psoriasis, and melanoma, as well as for assessing the percutaneous absorption of topical medications and measuring stratum corneum protein levels using a spectrophotometer.

A tape strip consists of a transparent plastic disc with an adhesive side. This disc is applied to a specified area of skin using forceps and is then pressed down with an instrument that exerts uniform pressure for a duration of between 2 to 10 seconds (Breternitz et al., 2007). Afterward, the disc is uniformly peeled off in one direction using forceps and placed into a container. Employing multiple sequential tape strips at the same site allows for more comprehensive removal of stratum corneum content. The number of tape strips required may vary depending on the anatomical location or specific skin conditions.

2.5.2 Protein Assay

Once the stratum corneum specimen has been collected, quantification is required. The colorimetric protein assay technique is an effective method to measure the quantity of the removed stratum corneum layer and assess the strength of intercellular cohesion. The protein assay involves immersing tape strips, which contain the stratum corneum layer, in a 1 molarity (M) of sodium chloride solution. This mixture is agitated for a set period to extract components, particularly the stratum corneum proteins. Subsequently, the extracted proteins are neutralized with 1 M hydrochloric acid and agitated again. The resulting solution, containing the stratum corneum proteins, is then stained using a dyeing agent, such as the Bradford or Lowry assay (Dreher et al., 1998). Quantification of the protein content on the tape strips is conducted using a spectrophotometer.

2.5.3 Spectrophotometer

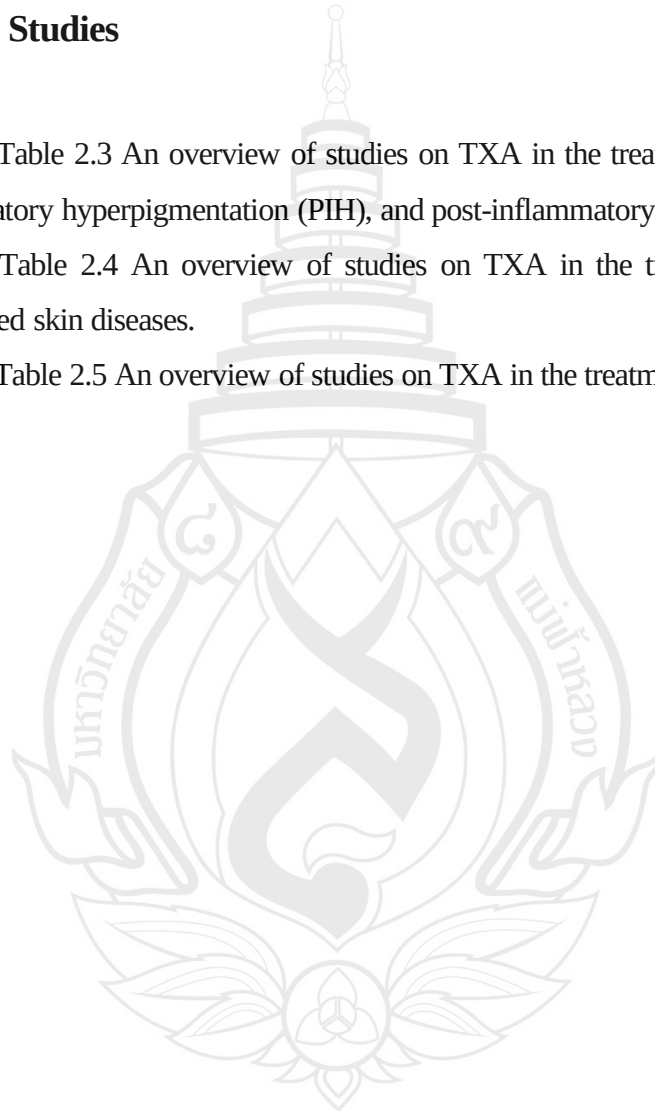
A spectrophotometer is an instrument designed to quantify the concentration of a substance by directing a beam of light at a specific wavelength through a colored sample and measuring the absorbance of light.

2.6 Related Studies

2.6.1 Table 2.3 An overview of studies on TXA in the treatment of acne vulgaris, post-inflammatory hyperpigmentation (PIH), and post-inflammatory erythema (PIE).

2.6.2 Table 2.4 An overview of studies on TXA in the treatment of rosacea or rosacea-induced skin diseases.

2.6.3 Table 2.5 An overview of studies on TXA in the treatment of melasma



CHAPTER 3

RESEARCH METHODOLOGY

3.1 Study Design

This study was a clinical trial designed with a double-blind, placebo-controlled, split-face methodology involving randomly selected subjects. Throughout the course of the research, neither the investigators nor the participants were aware of which product was administered to each side of the face, ensuring the objectivity and integrity of the results. The objective was to evaluate the efficacy of 15% TXA in inducing skin desquamation, treating acne, and reducing wrinkles. Additionally, the study aimed to assess the effects of TXA on transepidermal water loss (TEWL), sebum production, stratum corneum integrity, and TEWL under the chin, comparing these outcomes with those observed in a placebo.

3.2 Study Population

Thai female subjects, aged between 18 and 25 years, with mild to moderate facial acne.

3.3 Sample

Thai female subjects, aged between 18 and 25 years, received the treatment and were followed up at Mae Fah Luang University Hospital, Bangkok.

3.4 Sample Size Determination

The reference data source for sample size calculation in this research was the study titled “A Split-Face, Double-Blind, Randomized Study of the Efficacy of Green Tea Extract Cream in the Treatment of Acne Vulgaris” (Intarauthok, 2020), which involved 25 subjects.

The sample size was determined based on the number of inflammatory acne lesions observed over 12 weeks.

Calculating pooled variance (S_p^2)

$$S_p^2 = \frac{S_1^2 (n_1 - 1) + S_2^2 (n_2 - 1)}{n_1 + n_2 - 2}$$

S_p^2 = Pooled variance

S_1 = Standard deviation of the previous study at baseline (7.13)

S_2 = Standard deviation of the previous study after 12 weeks (6.88)

n_1 and n_2 = The number of reference's sample size (26)

$$S_p^2 = \frac{(7.13)^2(26-1) + (6.88)^2(26-1)}{(26 + 26 - 2)}$$

$$S_p^2 = 49$$

The sample size calculation (n)

$$n = \frac{S_p^2 [Z_{1-\alpha/2} + Z_\beta]^2}{(\mu_1 - \mu_2)^2}$$

S_p^2 = Pooled variance (49)

α = Type 1 error, two-tailed (0.05)

β = Type 2 error (0.80)

μ_1 = Mean value of at baseline (15.58)

μ_2 = Mean value after 12 weeks (10.31)

Z = Z-value, $Z_{1-\alpha/2} = Z_{1-0.05/2} = 1.96$

$Z_\beta = Z_{0.8} = 0.84$

$$n = \frac{(49) [1.96 + 0.84]^2}{(15.58 - 10.31)^2}$$

$$n = 13.8$$

$$n \approx 14$$

A 30% drop-off rate was considered in this study, resulting in a calculated sample size of 19 subjects (n=19).

3.5 Selection Criteria

3.5.1 Inclusion Criteria

- 3.5.1.1 Thai, healthy female subjects aged between 18 and 25 years.
- 3.5.1.2 Diagnosed with mild to moderate facial acne severity by a physician (Evaluator's Global Acne Severity Scale).
- 3.5.1.3 Willing to participate in the research study and sign the informed consent form.
- 3.5.1.4 Willing to follow the research guidelines as planned.

3.5.2 Exclusion Criteria

- 3.5.2.1 History of allergy to TXA products.
- 3.5.2.2 Positive patch test result for the 15% TXA product.
- 3.5.2.3 Positive patch test result for the placebo product.
- 3.5.2.4 History of intracranial bleeding, arterial or venous thromboembolism, active thromboembolic state, and defective color vision.
- 3.5.2.5 Current pregnancy or lactation or planning to conceive soon.
- 3.5.2.6 Current use of oral or injectable hormonal birth control.
- 3.5.2.7 Uncontrolled chronic diseases, including hypertension, diabetes mellitus, autoimmune diseases, cardiovascular diseases, kidney diseases, central nervous system diseases, and immunocompromised conditions.
- 3.5.2.8 History of active skin diseases, including atopic dermatitis, seborrheic dermatitis, or psoriasis.
- 3.5.2.9 History of sex hormone disorders, including polycystic ovarian syndrome, adrenocorticotrophic hormone, and Cushing's disease.
- 3.5.2.10 History of acne treatment within one month before participation in the research. The acne treatment could include the following:
 - 1. Topical treatments: retinoids, benzoyl peroxide, antibiotics, and chemical peels (AHA and BHA), for instance.

2. Systemic treatments: antibiotics (such as tetracycline, doxycycline, erythromycin, and amoxicillin), vitamin A, and combined oral contraceptives (COCs), for instance.

3. Other modalities: laser and visible light therapies.

3.5.3 Discontinuation Criteria

3.5.3.1 Subjects who intended to quit the study.

3.5.3.2 Subjects who developed severe complications during enrolment.

3.5.3.3 Subjects who failed to comply with the research guidelines and regulations.

3.5.3.4 Loss of follow-up.

3.6 Materials and Equipment

3.6.1 Information sheet

3.6.2 Informed consent

3.6.3 Patient record form and questionnaire

3.6.4 Investigator record form

3.6.5 Transparent plastic sheet

3.6.6 Permanent marker

3.6.7 VISIA[®] Skin Analysis System by Canfield Scientific, Inc.

3.6.8 Visioscan[®] VC98 Skin camera by Courage + Khazaka Electronic GmbH

3.6.9 Comeofix[®] F20 by Courage + Khazaka Electronic GmbH

3.6.10 Tewameter[®] TM300 (open chamber probe) by Courage + Khazaka Electronic GmbH

3.6.11 Sebumeter[®] SM815 by Courage + Khazaka Electronic GmbH

3.6.12 Multiprobe Adapter (MPA) by Courage + Khazaka Electronic GmbH

3.6.13 D100-D-Squame Standard Sampling Discs (22 mm D-Squame disc, Cliical & Derm)

3.6.14 D500-D-Squame Pressure Instrument (pressure 225 g/cm², D-Squame, Clinical & Derm)

3.6.15 Cryotubes (2 mL)

3.6.16 Refrigerator (-20 and -80 degrees Celsius)

3.6.17 Sodium hydroxide powder by Merk

3.6.18 Hydrochloric acid solution by Merk

3.6.19 Bradford dye reagent by Bio-Rad

3.6.20 Bovine serum albumin (BSA) standard solution (5mg/ml) by sigma

3.6.21 Adjustable speed laboratory horizontal shaker

3.6.22 Vortex-Genie 2 by Scientific Industries

3.6.23 Autopipettes with P200 and P1000

3.6.24 Tips (200 μ L and 1,000 μ L)

3.6.25 1.5 μ L microcentrifuge tubes

3.6.26 96-well plate by Nunc

3.6.27 Spectrophotometer with a wavelength of 595 nm by BioTek SYNERGY H1 microplate reader

3.6.28 15% tranexamic acid emulgel. The composition included ammonium acryloyldimethyltaurate/VP copolymer, glycerine, DI water, disodium EDTA, TXA, caprylic/capric triglyceride, phenoxyethanol, chlorphenesin, and glycerin. The emulgel is white in color with turbidity and pH 7.47. It came in a 15-gram plastic bottle. It was manufactured by Coursemetic Lab Co., Ltd.

3.6.29 Placebo emulgel. The composition included ammonium acryloyldimethyltaurate/VP copolymer, glycerine, DI water, disodium EDTA, caprylic/capric triglyceride, phenoxyethanol, chlorphenesin, and glycerin. The emulgel is white in color. The product was manufactured by Coursemetic Lab Co., Ltd. It was packaged in a 15-gram plastic bottle.

3.6.30 The facial cleansing agent was Acne Aid™ Gentle Cleanser

3.7 Study Procedures

3.7.1 Volunteers were enrolled based on the inclusion and exclusion criteria.

3.7.2 Volunteers were informed about the study objectives, procedures, benefits, precautions, guidelines for managing the side effects of the studied product, and general regulations.

3.7.3 Subjects signed the consent form at the start of the study.

3.7.4 Subjects provided general information, including patient history, underlying diseases, and acne-related details.

3.7.5 Subjects underwent patch tests for both the 15% TXA and placebo products on the volar aspect of their upper arm. After 48 hours, the allergic reactions were evaluated. Subjects who showed positive signs of an allergic reaction were excluded from the study before it began.

3.7.6 Subjects washed their face and the area under their chin with the provided facial cleanser (Acne Aid™ Gentle Cleanser) and patted dry with paper towels.

3.7.7 Subjects were required to acclimatize in a room at 25 degrees Celsius for 30 minutes.

3.7.8 Using the VISIA® Skin Analysis device, three photos were taken from multiple angles: a frontal view and left and right oblique views at 37-degree angles.

3.7.9 Acne counts and severity were assessed through physical examination, with lesions marked on a transparent plastic sheet for both sides of the face. This sheet was used to track old and new lesions over time. Two physicians who were not involved in the study conducted the evaluations at baseline.

3.7.10 The outer layer of the participants' facial skin was sampled using an adhesive tape (Corneofix® F 20) applied two fingerbreadths lateral to the corners of the mouth on both sides of the face. These adhesive tapes, containing the skin samples, were then photographed using the Visioscan® VC 98 camera for close-up image analysis and to measure the desquamation index.

3.7.11 Facial transepidermal water loss (TEWL) and sebum levels were measured three times per side on the forehead, cheek, and chin along the pupil line to obtain an average value. These measurements were taken using the Tewameter® TM300 (open chamber probe) and the Sebumeter® SM815, respectively.

3.7.12 Four out of nineteen subjects were randomly selected by a physician uninvolved in the study for stratum corneum (SC) removal under the chin area on both the right and left sides. The selection was performed using a 'True Random Number Generator' from the website <https://www.random.org> (RANDOM.ORG, 1998-2024). The generator selected numbers within the range of 0 to 19, corresponding to the order of the subjects involved in the study. The SC layer was collected using D100-D-Squame Standard Sampling Discs (22 mm) at week 0 for baseline and week 4 for analysis. Transepidermal water loss was measured before and after SC collection at the same location where the SC was removed.

3.7.12.1 The removal of the stratum corneum was conducted using 10 strips of D-squame adhesive discs on each side of the chin. Initially, a tape strip was applied to the confined area using forceps, positioned 0.5 cm away from the midline, which had been pre-marked to differentiate the left and right sides of the chin. A circular dashed line, slightly larger than the disc, was drawn around the tape using a marker to delineate the area for the tape stripping, as illustrated in Figure 3.1. The tape was then firmly pressed with a constant pressure of 225 g/cm² using a D500-D-squame pressure instrument for 10 seconds. It was then removed with forceps unidirectionally from top to bottom at a consistent speed of 2 seconds. The first tape strip was discarded due to potential contamination from environmental pollutants, skin flora, and skincare product residues. The process was repeated with a new adhesive tape, which was designated as tape strip no. 1 in the SC collection process. This procedure was repeated until 10 strips were collected on each side (Gorcea et al., 2013; Tagami, 2008). Each side was completed sequentially before moving on to the other. The collected SC samples were placed in 2 ml cryotubes, ensuring that the adhesive side containing the skin was facing upward. All samples were stored at -20 degrees Celsius for subsequent protein assay procedures at the Department of Microbiology, Faculty of Public Health, Mahidol University. (These procedures adhered to the guidelines established by (Hughes et al., 2021).



Source Hughes et al. (2021)

Figure 3.1 Tape Stripping Technique

3.7.12.2 TEWL was measured twice during this process. The first measurement was taken immediately before the stripping process, and the second measurement was taken

2 minutes after the final tape strip was removed. The 2-minute wait allowed the skin's water content to reach equilibrium and stabilize for an accurate measurement (Bashir et al., 2005; Bashir et al., 2001).

3.7.13 An uninvolved physician randomly selected which side of each subject's face would receive the TXA emulgel and which side would receive the placebo emulgel. This selection was made using a 'True Random Number Generator' from the website (RANDOM.ORG, 1998-2024). The generation of either an even or odd number (range: 0 to 19) determined the side of the face for the emulgel application.

An even number represented the right side. This meant 15% of TXA would be applied to the right side of the face, whereas the placebo would be applied to the left side.

An odd number represented the left side. This meant 15% of TXA would be applied to the left side of the face, whereas the placebo would be applied to the right side.

3.7.14 Subjects received a product kit containing two plastic tubes, one with TXA emulgel, the other with a placebo emulgel, and a small bottle of facial cleanser (Acne Aid™ Gentle Cleanser). The 15% TXA emulgel was provided in tube number 2, while the placebo emulgel was in tube number 1, as illustrated in Figure 3.2.



Figure 3.2 Characteristics of the Products

Product Application Instructions:

Step 1: Start with tube number 1. Squeeze the tube to release the emulgel onto the index finger, applying the amount from the distal crease to the tip of the finger twice (for a total of 2 finger-tip units, FTU), demonstrated in Appendix G. The finger holding the product should be on the same side of the face where the emulgel will be applied. One FTU is equal to the length from the distal crease to the end of the fingertip, as shown in Figure 3.3. One FTU dispenses 0.5 grams of the product.



Source Hon A/Prof Amanda Oakley (2001)

Figure 3.3 1 Fingertip Unit (FTU)

Step 2. Apply the product to the face, starting with the forehead, then the nose, cheek, chin, and under the chin area.

Step 3. Squeeze tube number 2 onto the other index finger and repeat the application process outlined in steps 1 and 2.

Step 4. Apply the products twice daily, once in the morning and once in the evening.

3.7.15 Subjects were permitted to use sunscreen and beauty products as usual during the study. However, they were strongly advised also to use additional sun protection measures, such as wearing a hat, carrying an umbrella, wearing sunglasses, or using a surgical mask for outdoor activities.

3.7.16 Subjects were informed in advance about the possible side effects, including dryness, redness, burning sensation, and exfoliation (the degree of skin exfoliation was

demonstrated in Appendix G). They were advised to report any occurrence of these side effects. If subjects could not tolerate the symptoms, they were instructed to stop using the product immediately and consult with the investigator for further treatment. Subjects who developed severe side effects would be withdrawn from the study

3.7.17 The follow-up evaluations were scheduled weekly for the first four weeks, with a final follow-up in the eighth week. During the fourth-week visit, the TXA treatment was switched to a placebo.

3.7.18 During the 4th week follow-up, SC removal using the tape stripping technique, along with pre-and post-TEWL measurements, was performed for the second time on the same subjects. The position for stratum corneum removal was relocated 0.5-1 cm to the lateral side from the original site.

3.7.19 The investigator collected all data for analysis. For the stratum corneum quantification, the collected samples would be further executed by protein assay and opacity measurement using a spectrophotometer at the Department of Microbiology, Faculty of Public Health, Mahidol University.

3.7.20 Protein Assay and Spectrophotometer

3.7.20.1 Methods for Protein Extraction

1. Add 500 μ L of 1M NaOH to the 2-mL cryotube containing the subjects' stratum corneum layers on D-Squame Standard Sampling disc (22 mm D-squame disc, Clinical & Derm)
2. Shake the tube on the horizontal shaker at 600 rpm for 2 hrs.
3. Add 500 μ L of 1M HCl to neutralize the solution.
4. Shake the tube on the shaking machine at 600 rpm for 15 mins.
5. Transfer the neutralized solution containing the extracted protein into a new 1.5-mL microcentrifuge tube.

6. Store extracted protein solution at -80 degrees Celsius for further analysis.

3.7.20.2 Methods for Protein Quantification

1. Gently mix the Bradford Reagent in the bottle and bring it to room temperature
2. Prepare a set of BSA standards containing 250, 125, 62.5, 31.25, 15.625, 7.8, and 3.9 μ g/mL in PBS, respectively) in separate tubes.

3. Add 80 μL of diluted BSA standards and extracted protein samples to the well of a 96-well plate. Extract solution is used as blank.
4. Add 20 μL of Bradford dye reagent and mix well.
5. Incubate at 37 degrees Celsius for 15 minutes.
6. Measure the absorbance at 595 nm by a spectrophotometer.
7. Compare the stratum corneum protein concentration to the standard curve prepared using the BSA protein standards.

3.8 Outcome Evaluation and Data Collection

3.8.1 Acne Lesion Counts and Acne Severity Grading

The number of acne lesion counts and severity were evaluated at baseline and weeks 1, 2, 3, 4, and 8.

3.8.1.1 Acne lesion counts

Acne lesions were counted and classified by type. Non-inflammatory acne was categorized into open and closed comedones, while inflammatory acne was categorized into papules, pustules, nodules, and cysts. The number of acne lesions was recorded for different areas of the face, as shown in Figure 3.4

	Right side of the Face						Left side of the Face					
	Forehead	Cheek	Nose	Chin	Under chin	Total no.	Forehead	Cheek	Nose	Chin	Under chin	Total no.
Non-inflammatory acne												
Closed												
Open												
Total no.												
Inflammatory acne												
Papules												
Pustules												
Nodules												
Cysts												
Total no.												

Right Side

Non-inflammatory acne count:

Inflammatory acne count:

Left Side

Non-inflammatory acne count:

Inflammatory acne count:

Figure 3.4 Acne Lesion Counts

3.8.1.2 Acne Severity Grade

The severity of acne was assessed for the entire half of the face. The Evaluator's Global Acne Severity Scale is shown in Table 2.1.

3.8.1.3 Acne Erythema Grading (The 4-point grading)

Erythema and the characteristics of resolving acne were evaluated using a 4-point grading scale for acne erythema, as shown in Table 2.2.

3.8.2 Desquamation

3.8.2.1 Physical Examination

Facial scales were clinically observed through physical examination. The findings were recorded as shown in Table 3.1.

Table 3.1 Scale

Score	Grade	Description
0	None	No scaling
1	Mild	Barely perceptible, fine scales present to limited areas of the face
2	Moderate	Fine scales generalized to all areas of the face
3	Severe	Scaling and peeling of skin over areas of the face

Source Callender et al. (2012)

3.8.2.2 Visoscan[®] VC 98

The Visoscan[®] VC 98 probe and Corneofix[®] F20 were used to capture images of the skin and stratum corneum layer, respectively. These images were taken at the corner of the mouth and two fingerbreadths laterally. Subsequently, the software program calculated the desquamation index.

3.8.2.3 Stratum Corneum Quantification

The stratum corneum layer under the chin on both sides was analyzed using a protein assay and opacity measurement with a spectrophotometer. The results were compared

between the TXA-treated and placebo sides at week 4 and against their respective baseline measurements.

3.8.3 Periorbital Wrinkle Assessment

3.8.3.1 Physical Examination

For clinical assessment of periorbital wrinkles, Fitzpatrick's Classification of Facial Wrinkling (Perioral and Periorbital), as described by Lemperle et al. (2001), was utilized. The details of this classification can be found in Table 3.2.

Table 3.2 Fitzpatrick's Classification of Facial Wrinkling (Perioral and Periorbital)

Class	Wrinkling	Degree of Elastosis
I	Fine wrinkles	Mild (fine textural changes with subtly accentuated skin lines)
II	Fine to moderate depth wrinkles, moderate number of lines	Moderate (distinct papular elastosis, individual papules with yellow translucency, dyschromia)
III	Fine to deep wrinkles, numerous lines, with or without redundant skin	Severe (multipapular and confluent elastosis, thickened yellow and pallid cutis rhomboidalis)

Source Lemperle et al. (2001)

3.8.3.2 VISIA®Skin Analysis System

Periorbital wrinkle assessment was evaluated into the score.

3.8.4 Transepidermal Water Loss (TEWL)

3.8.4.1 TEWL of the Face

TTEL was measured using a Tewameter[®] TM300 (open chamber probe) on three facial areas: the forehead, cheek, and chin, along the mid-pupil line. The results were reported as an average value for each half of the face.

3.8.4.2 TEWL Submental Area

The level of TEWL was measured under the chin area both before and after the stratum corneum layer was removed using the D-Squam disk.

3.8.5 Sebum Levels

Sebum levels were measured using a Sebumeter[®] SM815 in three facial areas: the forehead, cheek, and chin along the mid-pupil line. The results were reported as an average value for each half of the face.

3.8.6 Photos Analysis

Facial photo analysis was conducted using the multi-image VISIA[®] Skin Analysis system. The photos were evaluated for three key areas: anti-inflammatory effects, post-inflammatory hyperpigmentation of acne, and skin brightness and desquamation formation.

3.8.7 Side Effect Evaluation

Side effects were evaluated in 5 different areas: scaling, erythema, itching, burning, and stinging by the subjects at weeks 1, 2, 3, 4, and 8.

3.8.8 Satisfaction Evaluation

3.8.8.1 Satisfaction of treatment

Subjects assessed their satisfaction regarding acne reduction (both in terms of acne counts and severity), desquamation formation, sebum reduction, and the reduction of periorbital fine lines using a questionnaire.

3.8.8.2 Satisfaction with the TXA product

Subjects assessed their satisfaction with the product based on its properties.

3.9 Data Analyses

3.9.1 Descriptive Statistics

3.9.1.1 Qualitative data included general basic information, side effects, and satisfaction; they were expressed in numbers.

3.9.1.2 Quantitative data included the number and severity of acne, protein quantity, transepidermal water loss from the surface, and desquamation level. This was expressed as average, standard deviation, median, minimum, and maximum values, and interquartile range.

3.9.2 Inferential Statistics

3.9.2.1 Comparisons of the number and severity of acne lesions treated by the TXA and placebo. Compared within the same side of the face and between both sides of the face at weeks 0, 1, 2, 3, 4, and 8. By using repeated measure ANOVA.

3.9.2.2 Comparisons of the removed stratum corneum amount by the tapes treated with the TXA and placebo. Compared within the same side of the face and between both sides of the face at weeks 0 and 4.

3.9.2.3 Quantity of protein

1. For normally distributed data (Parametric data), the Paired t-test was used.
2. In the case of abnormal distribution of data (Nonparametric data): Wilcoxon signed-rank test was used.

3.9.2.4 The level of TEWL, sebum, acne counts, and severity

1. In the case of normally distributed data (Parametric data): Repeated measure ANOVA was used.
2. The Friedman test was used for an abnormal distribution of data (Nonparametric data).

3.9.2.5 Statistical significance value (significant value) was determined by p-value < 0.05 .

3.10 Ethical Considerations

This study was conducted under Good Clinical Practice (GCP) guidelines. This standard provided public assurance of the rights, safety, and well-being of the subjects. This study was conducted following approval from the Mae Fah Luang University Ethics Committee on Human Research, reference number EC 22001-20.

Generally, understanding and considerations were as follows:

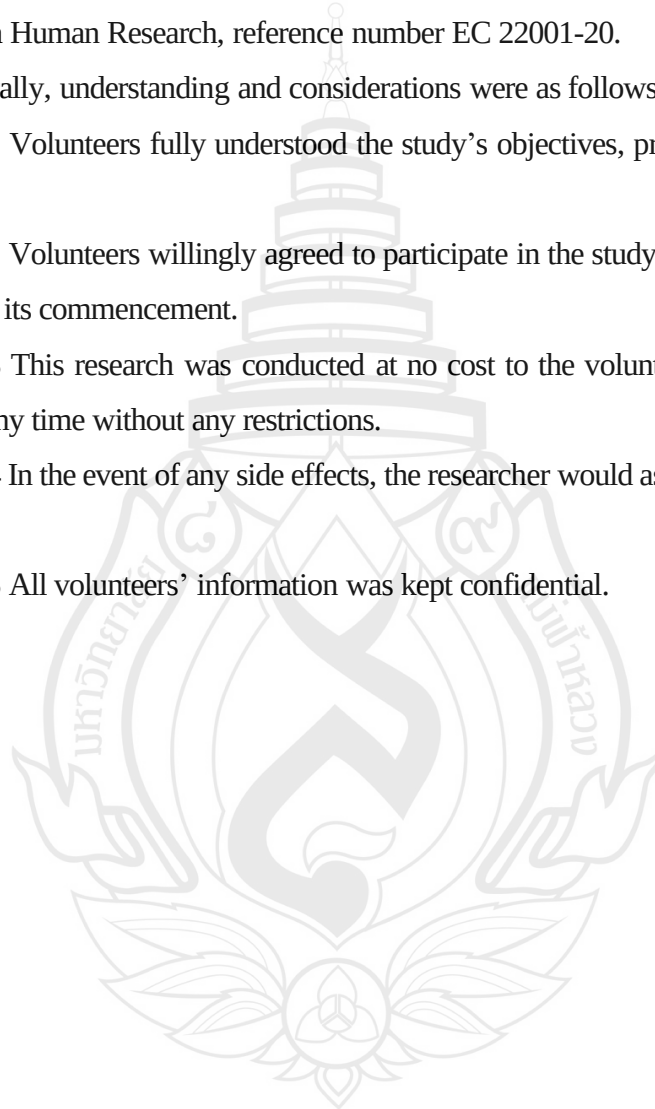
3.10.1 Volunteers fully understood the study's objectives, procedures, and potential side effects.

3.10.2 Volunteers willingly agreed to participate in the study and signed the consent forms prior to its commencement.

3.10.3 This research was conducted at no cost to the volunteers, who were free to withdraw at any time without any restrictions.

3.10.4 In the event of any side effects, the researcher would assist to the fullest extent possible.

3.10.5 All volunteers' information was kept confidential.



CHAPTER 4

RESULTS

The study was conducted to compare the outcomes of acne treatment, desquamation formation, and periorbital fine line reduction. Moreover, TEWL, Sebum, SC quantification, side effects, and satisfaction levels were evaluated after applying topical 15% TXA and topical placebo. The research results were presented as follows.

1. General characteristics of subjects
2. Comparison of non-inflammatory acne counts between tranexamic acid and placebo Treatments
3. Mean difference of non-inflammatory acne counts among time
4. Comparison of inflammatory acne counts between tranexamic acid and placebo treatments
5. Mean difference in inflammatory acne counts among time
6. Comparison of acne severity
7. Reduction in erythema of inflammatory papules
8. Comparison of desquamation index between tranexamic acid and placebo treatments
9. Comparison of transepidermal water loss (TEWL) between tranexamic acid and placebo treatments
10. Comparison of sebum production between tranexamic acid and placebo treatments
11. Comparison of stratum corneum quantities between tranexamic acid and placebo treatments
12. Submental transepidermal water loss (TEWL)
13. Comparison of periorbital wrinkle scores between tranexamic acid and placebo treatments Side effects evaluation
14. Satisfaction evaluation
15. Photos analysis and investigator evaluation

4.1 General Characteristics of Subjects

The study included nineteen participants, but 15 completed the study for the period of eight weeks at Mae Fah Luang University Hospital, Bangkok, from July 2022 to October 2022. Four volunteers discontinued since week 2 owing to travel constraints during the course of the study. The demographic data of all volunteers is demonstrated in Table 4.1. The study involved fifteen female participants, all residing in Bangkok. Out of fifteen, nine were between 22-25 years old, with a mean age of 22.73 ± 2.19 years. Their occupations included eight office workers, five students, and two government officers. According to the Fitzpatrick scale, skin type classification identified seven participants as type III, six as type IV, and two as type II. The predominant skin condition was oily, reported in seven subjects, followed by combination skin in five participants and dry skin in three. None of the subjects had any known underlying diseases or allergies to food and drugs.

Table 4.1 General Characteristics (n=15)

Characteristics	n
Age (years)	
Mean $\pm$ SD	22.73 ± 2.19
Min - Max	19 - 25
18-21	6
22-25	9
Gender	
Female	15
Male	0
Occupation	
Student	5
Officer	8
Government officer	2
Freelancer	0

Table 4.1 (continued)

Characteristics	n
Habitat	
BKK	15
Province	0
Fitzpatrick Skin Type	
I	0
II	2
III	7
V	0
Skin type	
Dry	3
Combination	5
Oily	7

Acne onset occurred between the ages of 15 and 19 for eleven participants, with a mean onset age of 17.07 ± 2.69 years. Ten participants experienced acne for a duration of 1 to 5 years, with a mean duration of 2.29 ± 2.18 years and an overall range of 0.08 to 9 years. Among these, five participants were identified with chronic acne. The primary contributing factors to acne development were oily skin and the menstrual cycle, each affecting seven participants. Additional factors included the use of surgical masks, implicated in six cases, and the use of cosmetics or skincare products in four cases. High-fat diets and environmental pollution each affected three participants. Twelve of the participants had undergone some form of acne treatment, predominantly topical therapies. Systemic therapies and laser or phototherapy were each utilized by four participants. Most cases were mild, involving twelve participants, while the remaining three experienced moderate acne. No severe acne cases were reported. The volunteer's medical history of acne vulgaris is demonstrated in Table 4.2.

Table 4.2 General Information of Subjects on Acne (n=15)

Characteristics	n
Age: onset of acne (years)	
Mean $\pm$ SD	17.07 $\pm$ 2.69
Min - Max	12 - 23
< 15	2
15-19	11
$\geq$ 20	2
Duration of acne (years)	
Mean $\pm$ SD	2.29 $\pm$ 2.18
Min - Max	0.08 – 9.00
1 -5	10
6 - 9	1
$\geq$ 10	0
Chronic acne	
No	10
yes	5
Influencing factors	
Oily skin type	7
High-fat diet	3
Cosmetics and skincare products	4
Menstrual cycle	7
Surgical mask	6
Environment	3
Previous acne treatment	
No	3
yes	12
Topical treatments	12
Systemic treatments	4
Laser/phototherapy	4

Table 4.2 (continued)

Characteristics	n
Others	10
Acne severity	
Mild	12
Moderate	3
Severe	0

4.2 Comparison of Non-Inflammatory Acne Counts Between Tranexamic Acid and Placebo Treatments

The study examining acne counts, specifically total non-inflammatory acne, closed comedones, and open comedones, demonstrated significant reductions in the 15% TXA group for total non-inflammatory acne at week 3 ($p=0.047$) and week 4 ($p=0.038$), as well as for closed comedones at week 4 ($p=0.025$). By week 8, both groups exhibited similar counts for total non-inflammatory acne and closed comedones. Throughout the study, no significant differences were observed in open comedones when comparing the two groups. However, a significant improvement was noted within the TXA group over time ($p=0.041$), as depicted in Table 4.3.

Table 4.3 Comparison of Total Non-Inflammatory Acne, Closed Comedones, and Open Comedones Counts Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean ± SD	Median (IQR)	Min-Max	Mean ± SD	Median (IQR)	Min-Max	
Total non-inflammatory acne							
Baseline	5.93 ± 2.55	7.00 (4.00,8.00)	1-9	6.60 ± 2.20	6.00 (5.50,8.50)	2-9	0.191
Week 1	5.93 ± 2.46	6.00 (4.00,8.00)	1-9	6.53 ± 2.39	7.00 (5.00,8.00)	2-11	0.199
Week 2	5.27 ± 2.25	6.00 (3.50,7.00)	1-8	6.20 ± 2.08	7.00 (5.50,7.50)	1-9	0.063
Week 3	5.40 ± 1.88	6.00 (4.50,7.00)	2-8	6.20 ± 1.82	6.00 (5.00,7.50)	3-9	0.047
Week 4	5.00 ± 1.89	5.00 (4.00,5.50)	2-9	5.93 ± 2.25	6.00 (4.00,8.00)	2-9	0.038
Week 8	5.67 ± 2.61	5.00 (3.50,7.50)	3-11	5.67 ± 2.44	6.00 (4.00,6.00)	2-11	1.000
P-value**	0.502			0.685			
Closed comedones							
Baseline	5.47 ± 2.45	6.00 (3.50,7.50)	1-9	6.33 ± 2.19	6.00 (5.50,8.00)	2-9	0.084
Week 1	5.60 ± 2.50	6.00 (4.00,7.50)	1-9	6.40 ± 2.50	6.00 (5.00,8.00)	2-11	0.118
Week 2	5.20 ± 2.34	6.00 (3.50,7.00)	1-8	6.13 ± 2.10	7.00 (5.00,7.50)	1-9	0.089
Week 3	5.33 ± 1.91	6.00 (4.00,7.00)	2-8	6.07 ± 1.91	6.00 (4.50,7.50)	3-9	0.068
Week 4	4.87 ± 1.77	5.00 (4.00,5.50)	2-8	5.80 ± 2.21	6.00 (4.00,8.00)	2-9	0.025
Week 8	5.67 ± 2.61	5.00 (3.50,7.50)	3-11	5.67 ± 2.44	6.00 (4.00,6.00)	2-11	1.000
P-value**	0.786			0.851			

Table 4.3 (continued)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean $\pm$ SD	Median (IQR)	Min-Max	Mean $\pm$ SD	Median (IQR)	Min-Max	
Open comedones							
Baseline	0.47 $\pm$ 0.92	0.00 (0.00,0.50)	0-3	0.27 $\pm$ 0.59	0.00 (0.00,0.00)	0-2	0.384
Week 1	0.33 $\pm$ 0.62	0.00 (0.00,0.50)	0-2	0.53 $\pm$ 1.55	0.00 (0.00,0.00)	0-6	0.595
Week 2	0.07 $\pm$ 0.26	0.00 (0.00,0.00)	0-1	0.07 $\pm$ 0.26	0.00 (0.00,0.00)	0-1	1.000
Week 3	0.07 $\pm$ 0.26	0.00 (0.00,0.00)	0-1	0.13 $\pm$ 0.35	0.00 (0.00,0.00)	0-1	0.582
Week 4	0.13 $\pm$ 0.35	0.00 (0.00,0.00)	0-1	0.13 $\pm$ 0.35	0.00 (0.00,0.00)	0-1	1.000
Week 8	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	1.000
P-value**	0.041			0.354			

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

4.3 Mean Difference of Non-inflammatory Acne Counts Among Time

The table below presents the mean differences in counts of open comedones over time. Notably, 15% TXA significantly reduced open comedones compared to baseline at multiple time points. Significant reductions were observed at weeks 2, 3, 4, and 8, with p-values of 0.018, 0.018, 0.046, and 0.006, respectively. No significant differences were noted in comparisons between subsequent time points, except from week 1 to week 8, where the p-value was 0.046, as shown in Table 4.4.

Table 4.4 Mean Difference in Open Comedones Counts Among Time with 15% Tranexamic Acid (n=15)

Comparisons among time	Mean difference of 15%Tranexamic acid	p-value*
Baseline – Week 1	- 0.13 ± 0.64	0.420
Baseline – Week 2	- 0.40 ± 0.91	0.018
Baseline – Week 3	- 0.40 ± 0.99	0.018
Baseline – Week 4	- 0.33 ± 0.82	0.046
Baseline – Week 8	- 0.47 ± 0.92	0.006
Week 1 – Week 2	- 0.27 ± 0.59	0.109
Week 1 – Week 3	- 0.27 ± 0.70	0.109
Week 1 – Week 4	- 0.20 ± 0.56	0.228
Week 1 – Week 8	- 0.33 ± 0.62	0.046
Week 2 – Week 3	- 0.00 ± 0.38	1.000
Week 2 – Week 4	0.07 ± 0.46	0.686
Week 2 – Week 8	- 0.07 ± 0.26	0.686
Week 3 – Week 4	0.07 ± 0.46	0.686
Week 3 – Week 8	- 0.07 ± 0.26	0.686
Week 4 – Week 8	- 0.13 ± 0.35	0.420

Note * signifies that the p-value was calculated by Paired t-test

4.4 Comparison of Inflammatory Acne Counts Between Tranexamic Acid and Placebo Treatments

The study of total inflammatory acne, papules, pustules, nodules, and cysts counts between the TXA and the placebo groups. Overall, there was an increasing trend in inflammatory acne counts, including its subtypes, in both the TXA and placebo groups. However, a significant reduction in total inflammatory acne count was observed at week 2 in the TXA group compared to the placebo group ($p=0.005$). Significant papule reductions were also noted at week 2 ($p=0.019$) and week 3 ($p=0.045$) in the TXA group compared to the placebo group. There were no significant differences in pustules, nodules, and cysts between the groups at any time point.

Significant within-group improvement was found in both the 15% TXA and the placebo groups for total inflammatory acne with $p=0.004$ and $p<0.001$, respectively. Moreover, in the papule subtypes, a significant improvement was found in the placebo group with $p<0.001$. All the information is demonstrated in Table 4.5.

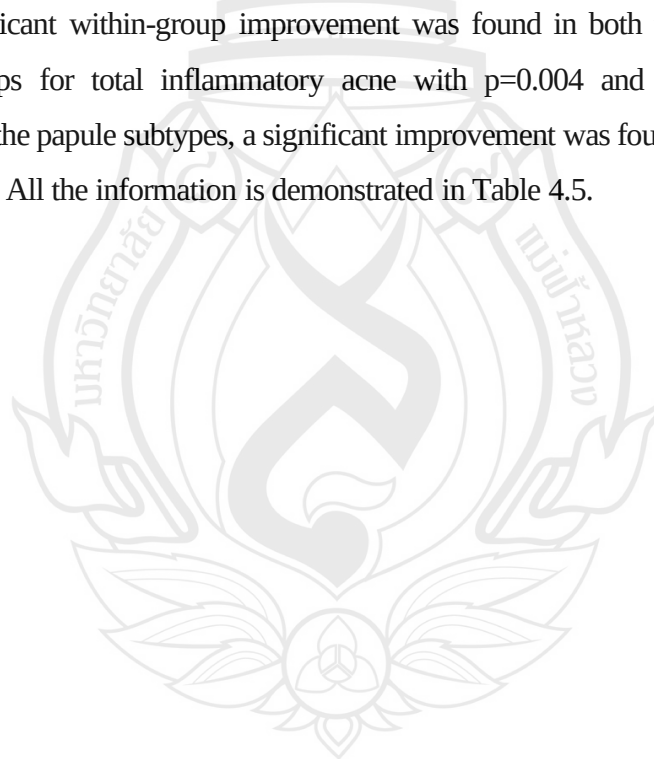


Table 4.5 Comparison of Total Inflammatory Acne, Papules, Pustules, Nodules, and Cysts Counts Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean ± SD	Median (IQR)	Min-Max	Mean ± SD	Median (IQR)	Min-Max	
Total inflammatory acne							
Baseline	2.33 ± 1.11	2.00 (2.00,3.00)	1-5	2.27 ± 1.22	2.00 (1.00,3.00)	1-4	0.719
Week 1	3.73 ± 2.60	3.00 (2.00,6.00)	0-9	4.13 ± 2.13	4.00 (2.50,5.00)	2-9	0.189
Week 2	4.20 ± 2.54	4.00 (2.50,5.00)	1-10	5.00 ± 2.90	5.00 (3.50,6.00)	0-12	0.005
Week 3	4.67 ± 4.22	3.00 (2.00,6.00)	1-14	5.20 ± 2.86	5.00 (3.50,7.50)	0-10	0.357
Week 4	4.60 ± 5.45	3.00 (1.00,5.00)	0-19	4.73 ± 3.67	5.00 (2.00,6.50)	0-13	0.834
Week 8	3.80 ± 3.17	3.00 (1.00,6.50)	0-9	3.93 ± 2.99	4.00 (1.50,6.00)	0-11	0.719
P-value**	0.004*			<0.001*			
Papules							
Baseline	2.27 ± 1.03	2.00 (2.00,3.00)	1-5	2.27 ± 1.22	2.00 (1.00,3.00)	1-4	1.000
Week 1	3.47 ± 2.47	3.00 (2.00,6.00)	0-8	3.67 ± 1.76	3.00 (2.00,4.00)	2-8	0.486
Week 2	3.93 ± 2.31	4.00 (2.50,4.50)	1-9	4.60 ± 3.04	5.00 (2.50,6.00)	0-12	0.019
Week 3	3.80 ± 3.65	3.00 (1.50,3.00)	1-12	5.00 ± 2.95	5.00 (3.00,7.50)	0-10	0.045
Week 4	3.80 ± 4.97	2.00 (1.00,3.50)	0-19	4.13 ± 3.09	3.00 (2.00,6.00)	0-10	0.660

Table 4.5 (continued)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean ± SD	Median (IQR)	Min-Max	Mean ± SD	Median (IQR)	Min-Max	
Week 8	3.53 ± 2.83	3.00 (1.00,6.00)	0-9	3.80 ± 2.91	4.00 (1.50,5.50)	0-11	0.334
P-value**	0.067			<0.001*			
Pustules							
Baseline	0.07 ± 0.26	0.00 (0.00,0.00)	0-1	0.00 ± 0.00	0.00 (0.00,0.00)	0-0	0.334
Week 1	0.13 ± 0.35	0.00 (0.00,0.00)	0-1	0.33 ± 0.62	0.00 (0.00,0.50)	0-2	0.082
Week 2	0.07 ± 0.26	0.00 (0.00,0.00)	0-1	0.20 ± 0.56	0.00 (0.00,0.00)	0-2	0.164
Week 3	0.20 ± 0.56	0.00 (0.00,0.00)	0-2	0.00 ± 0.00	0.00 (0.00,0.00)	0-0	0.334
Week 4	0.27 ± 0.80	0.00 (0.00,0.00)	0-3	0.20 ± 0.77	0.00 (0.00,0.00)	0-3	0.189
Week 8	0.13 ± 0.52	0.00 (0.00,0.00)	0-2	0.00 ± 0.00	0.00 (0.00,0.00)	0-0	0.334
P-value**	0.215			0.080			
Nodules							
Baseline	0.00 ± 0.00	0.00 (0.00,0.00)	0-0	0.00 ± 0.00	0.00 (0.00,0.00)	0-0	1.000
Week 1	0.13 ± 0.35	0.00 (0.00,0.00)	0-1	0.13 ± 0.35	0.00 (0.00,0.00)	0-1	1.000
Week 2	0.20 ± 0.56	0.00 (0.00,0.00)	0-2	0.20 ± 0.41	0.00 (0.00,0.00)	0-1	1.000
Week 3	0.27 ± 0.59	0.00 (0.00,0.00)	0-2	0.20 ± 0.56	0.00 (0.00,0.00)	0-2	1.000

Table 4.5 (continued)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean $\pm$ SD	Median (IQR)	Min-Max	Mean $\pm$ SD	Median (IQR)	Min-Max	
Week 4	0.47 $\pm$ 0.64	0.00 (0.00,1.00)	0-2	0.40 $\pm$ 0.63	0.00 (0.00,1.00)	0-2	0.334
Week 8	0.20 $\pm$ 0.41	0.00 (0.00,0.00)	0-1	0.13 $\pm$ 0.35	0.00 (0.00,0.00)	0-1	1.000
P-value**	0.424			1.000			
Cysts							
Baseline	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	1.000
Week 1	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	1.000
Week 2	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	1.000
Week 3	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	1.000
Week 4	0.07 $\pm$ 0.26	0.00 (0.00,0.00)	0-1	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	1.000
Week 8	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	0.00 $\pm$ 0.00	0.00 (0.00,0.00)	0-0	1.000
P-value**	1.000			1.000			

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

4.5 Mean Difference in Inflammatory Acne Counts Among Time

The table below presents the mean differences in total inflammatory acne counts between 15% TXA and placebo groups. In the 15% TXA group, significant improvements were noted at week 1 ($p=0.004$), week 2 ($p<0.001$), week 3 ($p=0.014$), and week 8 ($p=0.022$), with a non-significant change observed at week 4 ($p=0.068$). Conversely, the placebo group demonstrated a consistent significant increase from baseline at weeks 1, 2, and 3 (all $p<0.001$), week 4 ($p=0.002$), and week 8 ($p=0.006$). Additionally, significant changes within the placebo group were observed from week 1 to week 2 ($p=0.018$) and week 3 ($p=0.006$); from week 2 to week 8 ($p<0.001$); from week 3 to week 8 ($p<0.001$); and from week 4 to week 8 ($p=0.028$), as demonstrated in Table 4.6.

Table 4.6 Mean Difference in Total Inflammatory Acne Counts Among Time of 15% Tranexamic Acid and Placebo (n=15)

Comparisons among time	Mean difference of 15% Tranexamic acid	p-value*	Mean difference of Placebo	p-value*
Baseline – Week 1	1.40 ± 1.60	0.004	1.87 ± 1.19	<0.001
Baseline – Week 2	1.87 ± 1.51	<0.001	2.73 ± 1.94	<0.001
Baseline – Week 3	2.33 ± 3.20	0.014	2.93 ± 1.83	<0.001
Baseline – Week 4	2.27 ± 4.43	0.068	2.47 ± 2.59	0.002
Baseline – Week 8	1.47 ± 2.20	0.022	1.67 ± 2.00	0.006
Week 1 – Week 2	0.47 ± 0.92	0.068	0.87 ± 1.25	0.018
Week 1 – Week 3	0.93 ± 2.02	0.095	1.07 ± 1.28	0.006
Week 1 – Week 4	0.87 ± 3.40	0.340	0.60 ± 1.68	0.189
Week 1 – Week 8	0.07 ± 0.88	0.774	-0.20 ± 1.27	0.550
Week 2 – Week 3	0.47 ± 20.00	0.372	0.20 ± 0.94	0.424
Week 2 – Week 4	0.40 ± 3.04	0.619	-0.27 ± 1.33	0.452
Week 2 – Week 8	-0.40 ± 1.18	0.212	-1.07 ± 0.96	<0.001

Table 4.6 (continued)

Comparisons among time	Mean difference of 15% Tranexamic acid	p-value*	Mean difference of Placebo	p-value*
Week 3 – Week 4	-0.07 ± 1.94	0.896	-0.47 ± 1.41	0.220
Week 3 – Week 8	-0.87 ± 1.64	0.060	-1.27 ± 1.03	<0.001
Week 4 – Week 8	-0.80 ± 3.08	0.331	-0.80 ± 1.27	0.028

Note * signifies that the p-value was calculated by Paired t-test

The following table presents the mean differences in papule counts within the placebo group over an 8-week study period. There was a significant increase in acne counts from baseline at weeks 1, 2, and 3 (all, $p < 0.001$), week 4 ($p = 0.002$), and week 8 ($p = 0.008$). Furthermore, significant increases were also observed from week 1 to week 2 ($p = 0.025$) and week 3 ($p = 0.004$). Conversely, significant reductions in papule counts were noted from week 2 to week 8 ($p < 0.001$), week 3 to week 4 ($p = 0.001$), and week 4 to week 8 ($p < 0.001$), as detailed in Table 4.7.

Table 4.7 Mean Difference in Papule Counts Among Time in the Placebo Group (n=15)

Comparisons among time	Mean difference of Placebo	p-value*
Baseline – Week 1	1.40 ± 0.83	<0.001
Baseline – Week 2	2.33 ± 2.02	<0.001
Baseline – Week 3	2.73 ± 1.87	<0.001
Baseline – Week 4	1.87 ± 1.96	0.002
Baseline – Week 8	1.53 ± 1.92	0.008
Week 1 – Week 2	0.93 ± 1.44	0.025
Week 1 – Week 3	1.33 ± 1.50	0.004
Week 1 – Week 4	0.47 ± 1.51	0.250
Week 1 – Week 8	0.13 ± 1.30	0.698
Week 2 – Week 3	0.40 ± 0.91	0.111

Table 4.7 (continued)

Comparisons among time	Mean difference of Placebo	p-value*
Week 2 – Week 4	-0.47 ± 0.99	0.089
Week 2 – Week 8	-0.80 ± 0.56	<0.001
Week 3 – Week 4	-0.87 ± 0.83	0.001
Week 3 – Week 8	-1.20 ± 1.01	<0.001
Week 4 – Week 8	-0.33 ± 1.11	0.265

Note * signifies that the p-value was calculated by Paired t-test

The study shows the mean percentage changes in acne counts from baseline to weeks 1, 2, 3, 4, and 8 for total inflammatory acne in subjects treated with 15% TXA and placebo. In total inflammatory acne, the TXA group showed percentage changes from 40.33 ± 77.08% to 73.89 ± 37.91%, while the placebo group showed higher changes from 57.22 ± 84.57% to 136.11 ± 101.85%. The differences between the groups were not statistically significant, with p-values ranging from 0.059 to 0.463. This indicates that, while both treatments resulted in changes in acne counts, there were no significant differences between the 15% TXA and placebo groups, as demonstrated in Table 4.8.

Table 4.8 Mean Percentage Changes in Total Inflammatory Acne Among Time Between 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid	Placebo	p-value*
	Mean ± SD	Mean ± SD	
Total inflammatory acne			
Baseline - Week 1	45.89 ± 58.69	95.56 ± 50.87	0.059
Baseline - Week 2	73.89 ± 37.91	128.89 ± 98.09	0.064
Baseline - Week 3	70.89 ± 81.44	136.11 ± 101.85	0.072
Baseline - Week 4	54.78 ± 109.51	88.33 ± 75.97	0.115
Baseline - Week 8	40.33 ± 77.08	57.22 ± 84.57	0.463

Note * signifies that the p-value was calculated by Paired t-test

4.6 Comparison of Acne Severity

The severity of acne among subjects treated with 15% TXA and placebo was recorded at baseline and weeks 1, 2, 3, 4, and 8. Initially, most subjects exhibited mild acne, comprising thirteen subjects in the TXA group and eleven subjects in the placebo group, with the remaining subjects presenting moderate acne. By week 1, the distribution within both groups was similar, with eight subjects displaying mild acne and seven showing moderate acne. In week 2, the TXA group experienced a slight increase in severity, with seven subjects at mild, seven at moderate, and one at severe levels. Conversely, the placebo group exhibited increased severity, with three subjects at mild, eleven at moderate, and one at severe levels. By week 3, the TXA group showed slight improvement, with two subjects nearly clear, nine with mild, one with moderate, and three with severe acne. In contrast, the placebo group mainly remained moderate with eleven subjects, while three had mild and one had severe acne. At week 4, the TXA group had one subject nearly clear, six with mild, six with moderate, and two with severe acne. The placebo group presented a similar pattern with one subject nearly clear, six with mild, and five with moderate, but a higher proportion of severe cases in three subjects. By week 8, the TXA group showed no severe cases, with one subject nearly clear, eight with mild, and six with moderate acne. Meanwhile, the placebo group had two subjects nearly clear, six with mild, and six with moderate acne. Overall, both groups exhibited shifts in acne severity over time, with the TXA group demonstrating a trend towards less severe acne by week. The information is demonstrated in Table 4.9.

Table 4.9 Comparison of Acne Severity Over Time Between 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid, n						Placebo, n					
	Clear	Almost clear	Mild	Moderate	Severe	Very severe	Clear	Almost clear	Mild	Moderate	Severe	Very severe
Baseline	-	-	13	2	-	-	-	-	11	4	-	-
Week 1	-	-	8	7	-	-	-	-	8	7	-	-
Week 2	-	-	7	7	1	-	-	-	3	11	1	-
Week 3	-	2	9	1	3	-	-	-	3	11	1	-
Week 4	-	1	6	6	2	-	-	1	6	5	3	-
Week 8	-	1	8	6	-	-	-	2	6	6	-	-

The following table compares acne severity between the 15% TXA and the placebo groups over time. At baseline, the mean severity scores were similar between the two groups, with the TXA group at 2.13 ± 0.35 and the placebo group at 2.27 ± 0.46 , showing no significant difference ($p=0.334$). By week 1, both groups had identical mean severity scores of 2.47 ± 0.52 ($p=1.000$). In week 2, the mean severity score for the TXA group was 2.60 ± 0.63 , slightly lower than the placebo group, which was 2.87 ± 0.52 , but this difference was not statistically significant ($p=0.217$). By week 3, the TXA group showed a lower mean severity score of 2.33 ± 0.98 compared to the placebo group's 2.87 ± 0.52 , approaching statistical significance ($p=0.056$). In week 4, the severity scores were 2.60 ± 0.83 for the TXA group and 2.73 ± 0.88 for the placebo group, with no significant difference ($p=0.499$). By week 8, the scores were 2.33 ± 0.62 for the TXA group and 2.40 ± 0.83 for the placebo group, again showing no significant difference ($p=0.670$). Overall, while there were some variations in severity scores over time, no significant differences were observed between the two groups. On the other hand, the placebo group exhibited a significant within-group change over time with $p = 0.021$, as demonstrated in Table 4.10.

Table 4.10 Comparison of Acne Severity Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid	Placebo	p-value*
	Mean $\pm$ SD	Mean $\pm$ SD	
Baseline	2.13 ± 0.35	2.27 ± 0.46	0.334
Week 1	2.47 ± 0.52	2.47 ± 0.52	1.000
Week 2	2.60 ± 0.63	2.87 ± 0.52	0.217
Week 3	2.33 ± 0.98	2.87 ± 0.52	0.056
Week 4	2.60 ± 0.83	2.73 ± 0.88	0.499
Week 8	2.33 ± 0.62	2.40 ± 0.83	0.670
P-value**	0.176	0.021	

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

The following table shows the mean difference in acne severity of the placebo group. The severity of acne over time revealed a significant increase from baseline to weeks 2 ($p=0.002$) and 3 ($p=0.007$) but no significant changes in other weeks. Additionally, significant increases were noted between week 1 and weeks 2 and 3 (both with $p=0.009$). Comparisons between later weeks showed no significant differences, indicating that the most notable changes occurred in the earlier weeks of the study, as demonstrated in Table 4.11.

Table 4.11 Mean Difference in Acne Severity Among Time in the Placebo Group (n=15)

Comparisons among time	Mean difference of Placebo	p-value*
Baseline – Week 1	0.20 ± 0.78	0.334
Baseline – Week 2	0.60 ± 0.63	0.002
Baseline – Week 3	0.60 ± 0.74	0.007
Baseline – Week 4	0.47 ± 1.06	0.110
Baseline – Week 8	0.13 ± 0.99	0.610
Week 1 – Week 2	0.40 ± 0.51	0.009
Week 1 – Week 3	0.40 ± 0.51	0.009
Week 1 – Week 4	0.67 ± 0.96	0.301
Week 1 – Week 8	0.07 ± 0.80	0.751
Week 2 – Week 3	-0.00 ± 0.54	1.000
Week 2 – Week 4	-0.13 ± 0.92	0.582
Week 2 – Week 8	-0.47 ± 0.92	0.068
Week 3 – Week 4	-0.13 ± 0.74	0.499
Week 3 – Week 8	-0.47 ± 0.92	0.068
Week 4 – Week 8	-0.33 ± 1.11	0.265

Note * signifies that the p-value was calculated by Paired t-test

4.7 Reduction in Erythema of Inflammatory Papules

The study of erythema reduction in inflammatory papules over time for subjects using 15% TXA and a placebo. At baseline, most subjects in both groups exhibited mild erythema, with thirteen subjects in the TXA group and fourteen subjects in the placebo group. By week 1, some subjects in both groups demonstrated no erythema, with four subjects in the TXA group and three in the placebo group. By week 2, all participants in the TXA group exhibited no erythema; in the placebo group, ten subjects had no erythema, and five subjects had mild erythema. From week three onwards, all subjects in both groups exhibited no erythema, indicating a complete resolution of the inflammatory acne. The information is demonstrated in Table 4.12.

Table 4.12 Comparison of Erythema Levels in Inflammatory Papules Over Time Between 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid, n				Placebo, n			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Baseline	-	13	2	-	-	14	1	-
Week 1	4	11	-	-	3	10	2	-
Week 2	15	-	-	-	10	5	-	-
Week 3	15	-	-	-	15	-	-	-
Week 4	15	-	-	-	15	-	-	-
Week 8	15	-	-	-	15	-	-	-

Comparisons of erythema reduction of the inflammatory papules between subjects using 15% TXA and placebo over 8 weeks. At baseline, the mean erythema levels were similar between the two groups, with 15% TXA at 1.13 ± 0.35 and placebo at 1.07 ± 0.26 ($p=0.334$). By week 1, there was a trend towards lower erythema in the TXA group (0.73 ± 0.46) compared to placebo (0.93 ± 0.59), although not statistically significant ($p=0.189$). However, by week 2, the TXA group showed a significant reduction in erythema (0.00 ± 0.00) compared to placebo (0.33 ± 0.49), with a p-value of 0.019. From week 3 onwards until

the end of the study, both groups exhibited no erythema, and there were no significant differences in erythema levels between the two groups. When comparing the erythema reduction within the TXA and the placebo groups over time, both exhibited significant differences with $p < 0.001$, as illustrated in Table 4.13.

Table 4.13 Comparison of Erythema Levels in Inflammatory Papules Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid	Placebo	p-value*
	Mean $\pm$ SD	Mean $\pm$ SD	
Baseline	1.13 $\pm$ 0.35	1.07 $\pm$ 0.26	0.334
Week 1	0.73 $\pm$ 0.46	0.93 $\pm$ 0.59	0.189
Week 2	0.00 $\pm$ 0.00	0.33 $\pm$ 0.49	0.019
Week 3	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	1.000
Week 4	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	1.000
Week 8	0.00 $\pm$ 0.00	0.00 $\pm$ 0.00	1.000
P-value**	<0.001	<0.001	

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

The following table presents the mean differences in erythema levels of inflammatory papules between the TXA and placebo groups, revealing significant reductions for both. Specifically, the 15% TXA group showed significant decreases from baseline at week 1 ($p=0.009$) and continued to show significant reductions through weeks 2, 3, 4, and 8 (all with $p < 0.001$). The placebo group demonstrated significant decreases starting from week 2 ($p < 0.001$) and persisting through weeks 3, 4, and 8 (all with $p < 0.001$). Subsequent weekly comparisons within each group indicated significant reductions from week 1 to later weeks (all with $p < 0.001$). Interestingly, while the 15% TXA group showed no significant changes from weeks 2 to the subsequent weeks, the placebo group exhibited significant reductions

from week 2 to weeks 3, 4, and 8 (all with $p=0.019$), with no further changes noted from week 3 onwards.

Table 4.14 Mean Difference in Acne Erythema Levels Among Time Between 15% Tranexamic Acid and Placebo Groups (n=15)

Comparisons among time	Mean difference of 15% Tranexamic acid	p-value*	Mean difference of Placebo	p-value*
Baseline – Week 1	-0.40 ± 0.51	0.009	-0.13 ± 0.52	0.334
Baseline – Week 2	-1.13 ± 0.35	<0.001	-0.73 ± 0.46	<0.001
Baseline – Week 3	-1.13 ± 0.35	<0.001	-1.07 ± 0.26	<0.001
Baseline – Week 4	-1.13 ± 0.35	<0.001	-1.07 ± 0.26	<0.001
Baseline – Week 8	-1.13 ± 0.35	<0.001	-1.07 ± 0.26	<0.001
Week 1 – Week 2	-0.73 ± 0.46	<0.001	-0.60 ± 0.51	<0.001
Week 1 – Week 3	-0.73 ± 0.46	<0.001	-0.93 ± 0.59	<0.001
Week 1 – Week 4	-0.73 ± 0.46	<0.001	-0.93 ± 0.59	<0.001
Week 1 – Week 8	-0.73 ± 0.46	<0.001	-0.93 ± 0.59	<0.001
Week 2 – Week 3	-0.00 ± 0.00	1.000	-0.33 ± 0.49	0.019
Week 2 – Week 4	-0.00 ± 0.00	1.000	-0.33 ± 0.49	0.019
Week 2 – Week 8	-0.00 ± 0.00	1.000	-0.33 ± 0.49	0.019
Week 3 – Week 4	-0.00 ± 0.00	1.000	-0.00 ± 0.00	1.000
Week 3 – Week 8	-0.00 ± 0.00	1.000	-0.00 ± 0.00	1.000
Week 4 – Week 8	-0.00 ± 0.00	1.000	-0.00 ± 0.00	1.000

Note * signifies that the p-value was calculated by Paired t-test

4.8 Comparison of Desquamation Index Between Tranexamic Acid and Placebo Treatments

The study assessed the desquamation index (DI) in subjects treated with 15% TXA compared to a placebo. Initially, baseline mean DI scores were virtually identical between the two groups, with the TXA group recording a DI of 34.91 ± 1.34 and the placebo group 34.97 ± 1.19 , indicating no significant difference ($p=0.788$). By week 1, the mean DI score in the TXA group slightly increased to 35.13 ± 1.43 , whereas the placebo group recorded 34.81 ± 1.70 , still showing no significant difference ($p=0.375$). At week 2, the TXA group's mean DI rose to 35.37 ± 1.12 , compared to 34.77 ± 1.53 in the placebo group, again with no significant difference ($p=0.124$). However, significant differences emerged between weeks 3 and 4. At week 3, the mean DI score was 35.88 ± 1.16 in the TXA group and 34.62 ± 1.70 in the placebo group ($p=0.035$). By week 4, the mean DI in the TXA group increased to 36.20 ± 1.29 , significantly higher than the placebo group's 34.57 ± 1.65 ($p=0.014$). By week 8, differences between the groups were insignificant, with the TXA group at 34.87 ± 1.59 and the placebo group at 34.53 ± 1.73 ($p=0.602$). However, significant intra-group differences were observed in the TXA group across the study period ($p<0.001$), as documented in Table 4.15.

Table 4.15 Comparison of Desquamation Index Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean $\pm$ SD	Median (IQR)	Min-Max	Mean $\pm$ SD	Median (IQR)	Min-Max	
Baseline	34.91 ± 1.34	34.29 (33.99,36.05)	33.08-36.84	34.97 ± 1.19	34.68 (33.95,36.09)	33.39-36.99	0.788
Week 1	35.13 ± 1.43	34.65 (34.38,35.64)	33.60-38.64	34.81 ± 1.70	34.1 (33.65,35.4)	32.73-37.86	0.375
Week 2	35.37 ± 1.12	35.38 (34.58,35.96)	33.84-37.54	34.77 ± 1.53	34.21 (33.89,35.62)	31.94-37.23	0.124
Week 3	35.88 ± 1.16	35.88 (35.16,36.72)	33.76-37.99	34.62 ± 1.70	34.21 (33.77,35.03)	31.84-38.08	0.035

Table 4.15 (continued)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean $\pm$ SD	Median (IQR)	Min-Max	Mean $\pm$ SD	Median (IQR)	Min-Max	
Week 4	36.20 $\pm$ 1.29	36.07 (35.23,37.04)	34.37-38.68	34.57 $\pm$ 1.65	34.33 (33.77,35.25)	31.38-38.05	0.014
Week 8	34.87 $\pm$ 1.59	34.64 (34.07,35.62)	31.03-37.47	34.53 $\pm$ 1.73	34.59 (33.94,35.26)	30.69-38.19	0.602
P-value**	<0.001			0.536			

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

The following table presents the mean difference in the desquamation index in the TXA group over time. From baseline, significant increases in desquamation were observed at week 2 ($p=0.037$), week 3 ($p=0.010$), and week 4 ($p=0.005$), with no significant change noted at week 8. When comparing week 1 to subsequent weeks, significant increases were noted at week 3 ($p=0.009$) and week 4 ($p=0.003$), but not at week 8. Comparisons from week 2 showed significant increases only at week 4 ($p=0.011$). Significant changes from week 3 were noted in both week 4 ($p=0.037$) and week 8 ($p=0.022$). Additionally, a significant decrease in desquamation was observed from week 4 to week 8 ($p=0.003$), as demonstrated in Table 4.16.

Table 4.16 Mean Difference in the Desquamation Index Among Time in the 15% Tranexamic Acid Group (n=15)

Comparisons among time	Mean difference of 15%Tranexamic acid	p-value*
Baseline – Week 1	0.23 $\pm$ 0.85	0.321
Baseline – Week 2	0.46 $\pm$ 0.77	0.037
Baseline – Week 3	0.98 $\pm$ 1.27	0.010
Baseline – Week 4	1.29 $\pm$ 1.49	0.005

Table 4.16 (continued)

Comparisons among time	Mean difference of 15% Tranexamic acid	p-value*
Baseline – Week 8	-0.04 ± 1.97	0.935
Week 1 – Week 2	0.24 ± 0.97	0.362
Week 1 – Week 3	0.75 ± 0.95	0.009
Week 1 – Week 4	1.07 ± 1.15	0.003
Week 1 – Week 8	-0.27 ± 1.74	0.561
Week 2 – Week 3	0.51 ± 1.01	0.070
Week 2 – Week 4	0.83 ± 1.10	0.011
Week 2 – Week 8	-0.50 ± 1.37	0.176
Week 3 – Week 4	0.32 ± 0.53	0.037
Week 3 – Week 8	-1.02 ± 1.53	0.022
Week 4 – Week 8	-1.33 ± 1.43	0.003

Note * signifies that the p-value was calculated by Paired t-test

4.9 Comparison of Transepidermal Water Loss (TEWL) Between Tranexamic Acid and Placebo Treatments

The study provides data on transepidermal water loss (TEWL) for subjects treated with 15% TXA compared to a placebo. Initially, at baseline, both groups had similar mean TEWL levels, with the TXA group at 15.58 ± 4.52 and the placebo group at 15.73 ± 4.33 , indicating no significant difference ($p=0.490$). Over the first eight weeks, the mean TEWL levels between the two groups showed slight variations without statistically significant differences ($p>0.05$). However, at weeks 3 and 4, the TXA group's mean TEWL was significantly higher than those in the placebo group, with p-values of 0.013 and less than 0.001, respectively. Additionally, within-group comparisons revealed significant changes in mean TEWL for both the TXA and placebo groups, both with p-values less than 0.001, as demonstrated in Table 4.17.

Table 4.17 Comparisons of Transepidermal Water Loss (TEWL) Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean $\pm$ SD	Median (IQR)	Min-Max	Mean $\pm$ SD	Median (IQR)	Min-Max	
Baseline	15.58 $\pm$ 4.52	16.40 (11.95,17.35)	8.20-23.50	15.73 $\pm$ 4.33	15.78 (11.93,18.18)	9.48-23.28	0.490
Week 1	15.81 $\pm$ 4.95	15.80 (11.80,19.55)	8.80-23.90	15.58 $\pm$ 4.10	15.90 (12.75,17.80)	9.30-23.60	0.606
Week 2	16.03 $\pm$ 4.36	16.00 (12.70,18.55)	9.10-24.00	15.37 $\pm$ 3.95	15.80 (13.25,17.50)	9.10-23.00	0.211
Week 3	16.52 $\pm$ 4.50	16.40 (12.85,19.60)	9.40-24.20	15.14 $\pm$ 3.84	15.50 (12.95,16.85)	8.70-22.60	0.013
Week 4	16.90 $\pm$ 4.42	17.00 (12.80,19.95)	10.20-24.50	14.90 $\pm$ 3.82	15.20 (12.70,16.60)	8.50-22.30	<0.001
Week 8	15.15 $\pm$ 3.92	15.40 (12.17,16.62)	8.57-22.37	14.60 $\pm$ 3.81	14.64 (11.95,16.29)	8.44-22.14	0.055
P-value**	<0.001			<0.001			

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

The following table presents the mean difference in transepidermal water loss (TEWL) between the 15% TXA and placebo groups across different time points. In the TXA group, significant increases were observed from baseline to week 3 ($p=0.011$) and week 4 ($p<0.001$); and from week 1 to week 3 ($p=0.033$) and 4 ($p=0.012$). Additionally, from week 2 to week 3 ($p=0.015$) and 4 ($p=0.020$), further increases were noted. Significant decreases were recorded from week 3 to week 8 ($p=0.007$) and from week 4 to week 8 ($p<0.001$). For the placebo group, significant decreases were observed from baseline to week 4 ($p=0.021$) and week 8 ($p=0.006$). There were also decreases from week 1 to week 3 ($p=0.011$), weeks 4 and 8 (both with $p<0.001$). Additionally, significant decreases were seen from week 2 to week 3 ($p=0.005$), weeks 4 and 8 (both with $p<0.001$), and from week 3 to week 4 and 8 (both with $p<0.001$). Lastly, from week 4 to week 8, a significant decrease was also noted ($p=0.022$), as demonstrated in Table 4.18.

Table 4.18 Mean Difference in TEWL Among Time Between 15% Tranexamic Acid and Placebo (n=15)

Comparisons among time	Mean difference of 15% Tranexamic acid		Mean difference of Placebo	
		p-value*		p-value*
Baseline – Week 1	0.23 ±1.64	0.591	-0.15 ±1.02	0.586
Baseline – Week 2	0.45 ±1.48	0.262	-0.35 ±1.23	0.284
Baseline – Week 3	0.94 ±1.24	0.011	-0.59 ±1.21	0.081
Baseline – Week 4	1.32 ±1.12	<0.001	-0.83 ±1.23	0.021
Baseline – Week 8	-0.43 ±1.00	0.116	-1.13 ±1.36	0.006
Week 1 – Week 2	0.21 ±1.31	0.538	-0.21 ±0.54	0.157
Week 1 – Week 3	0.71 ±1.16	0.033	-0.44 ±0.58	0.011
Week 1 – Week 4	1.09 ±1.46	0.012	-0.68 ±0.58	<0.001
Week 1 – Week 8	-0.67 ±2.07	0.235	-0.98 ±0.74	<0.001
Week 2 – Week 3	0.49 ±0.69	0.015	-0.23 ±0.27	0.005
Week 2 – Week 4	0.87 ±1.29	0.020	-0.47 ±0.29	<0.001
Week 2 – Week 8	-0.88 ±1.76	0.074	-0.77 ±0.57	<0.001
Week 3 – Week 4	0.38 ±0.94	0.138	-0.24 ±0.08	<0.001
Week 3 – Week 8	-1.37 ±1.68	0.007	-0.54 ±0.49	<0.001
Week 4 – Week 8	-1.75 ±1.54	<0.001	-0.30 ±0.45	0.022

Note * signifies that the p-value was calculated by Paired t-test

4.10 Comparison of Sebum Production Between Tranexamic Acid and Placebo Treatments

The study compares sebum production between groups treated with 15% TXA and a placebo. Initially, at baseline, the mean sebum levels were similar between the two groups, with 128.93 ± 52.97 for the TXA group and 128.60 ± 52.70 for the placebo group ($p=0.311$). By week 2, the mean sebum level in the TXA group (125.50 ± 53.31) was significantly lower than that in the placebo group (127.41 ± 51.87), with a p-value of 0.039.

This trend continued at week 4, where the TXA group (123.16 ± 52.77) also showed a significantly lower mean sebum level than the placebo (125.78 ± 52.85), with a p-value of 0.002. No significant differences were observed at week 1 ($p = 0.696$), week 3 ($p = 0.119$), or week 8 ($p=0.720$). However, within the TXA and the placebo groups, significant changes in mean sebum levels were noted, with p-values less than 0.001 and 0.008, respectively. Overall, the TXA group demonstrated significantly lower mean sebum levels at weeks 2 and 4 compared to the placebo group, and both groups showed significant changes within the group, as illustrated in Table 4.19.

Table 4.19 Comparison of Sebum Levels Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid			Placebo			p-value *
	Mean $\pm$ SD	Median (IQR)	Min-Max	Mean $\pm$ SD	Median (IQR)	Min-Max	
Baseline	128.93 $\pm$ 52.97	99.00 (79.83,183.33)	67.67-186.00	128.60 $\pm$ 52.70	98.67 (81.00,182.33)	67.33-185.33	0.311
Week 1	127.84 $\pm$ 53.40	98.97 (78.30,181.80)	62.97-186.30	128.27 $\pm$ 52.05	98.67 (80.17,181.50)	70.00-185.00	0.696
Week 2	125.50 $\pm$ 53.31	94.50 (77.33,179.67)	62.50-182.50	127.41 $\pm$ 51.87	97.23 (80.90,180.07)	68.57-183.57	0.039
Week 3	124.27 $\pm$ 53.23	92.91 (76.58,178.41)	62.58-182.58	126.62 $\pm$ 51.54	93.78 (78.61,179.78)	65.45-183.45	0.119
Week 4	123.16 $\pm$ 52.77	91.85 (75.51,176.51)	61.51-179.85	125.78 $\pm$ 52.85	97.42 (76.65,179.42)	64.42-185.42	0.002
Week 8	124.54 $\pm$ 53.13	90.26 (74.92,178.59)	65.26-184.26	125.11 $\pm$ 52.88	96.40 (77.74,181.40)	64.74-186.07	0.720
P-value**	<0.001			0.008			

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

The following table displays the mean differences in sebum production at various time points between the 15% TXA and the placebo groups. In the TXA group, notable decreases in sebum levels were recorded from baseline to week 1 ($p=0.036$), week 2, 3, 4, and 8 (all with $p<0.001$). Additional significant reductions were seen from week 1 to week 2

($p=0.002$), weeks 3 and 4 (both with $p<0.001$), and week 8 ($p=0.003$). There were also significant decreases from week 2 to week 3 ($p=0.003$) and week 4 ($P<0.001$), and from week 3 to week 4 ($p=0.001$). In the placebo group, significant reductions in sebum production were observed from baseline to week 2 ($p=0.048$), week 4 ($p<0.001$), and week 8 ($p=0.007$). There were also reductions from week 1 to week 4 ($p=0.009$) and week 8 ($p=0.016$), and from week 2 to week 4 ($p=0.016$). No significant differences were found between week 3 and week 8 or between week 4 and week 8 in either group. The information is illustrated in Table 4.20.

Table 4.20 Mean Difference in Sebum Levels Among Time Between 15% Tranexamic Acid and Placebo (n=15)

Comparisons among time	Mean difference of 15% Tranexamic acid	p- value*	Mean difference of Placebo	p- value*
Baseline – Week 1	-1.10 ± 1.83	0.036	-0.33 ± 2.59	0.626
Baseline – Week 2	-3.43 ± 1.91	<0.001	-1.19 ± 2.13	0.048
Baseline – Week 3	-4.67 ± 2.03	<0.001	-1.98 ± 4.07	0.081
Baseline – Week 4	-5.78 ± 2.13	<0.001	-2.82 ± 2.63	<0.001
Baseline – Week 8	-4.39 ± 3.34	<0.001	-3.49 ± 4.28	0.007
Week 1 – Week 2	-2.34 ± 2.33	0.002	-0.85 ± 2.63	0.228
Week 1 – Week 3	-3.57 ± 2.55	<0.001	-1.64 ± 4.34	0.164
Week 1 – Week 4	-4.68 ± 2.53	<0.001	-2.48 ± 3.20	0.009
Week 1 – Week 8	-3.29 ± 3.47	0.003	-3.15 ± 4.48	0.016
Week 2 – Week 3	-1.24 ± 1.35	0.003	-0.79 ± 4.45	0.504
Week 2 – Week 4	-2.34 ± 1.49	<0.001	-1.63 ± 2.30	0.016
Week 2 – Week 8	-0.96 ± 3.00	0.236	-2.30 ± 5.42	0.123
Week 3 – Week 4	-1.11 ± 1.08	0.001	-0.84 ± 5.19	0.541
Week 3 – Week 8	0.28 ± 3.03	0.727	-1.51 ± 5.79	0.330
Week 4 – Week 8	1.39 ± 3.05	0.100	-0.67 ± 4.98	0.610

Note * signifies that the p-value was calculated by Paired t-test

4.11 Comparison of Stratum Corneum Quantities Between Tranexamic Acid and Placebo Treatments

Four out of fifteen participants were randomly selected to collect the superficial layer of skin (stratum corneum layer) through a tape stripping technique on each side under the chin, where 15% TXA and placebo emulgel were applied at baseline and week 4. However, we could only get the results of 3 samples as one sample had a problem and could not obtain the result during the protein extraction. At baseline, the mean stratum corneum collected was nearly identical between the two groups, with the TXA side at 46.49 ± 15.14 and the placebo side at 46.45 ± 9.45 , with a negligible mean difference of 0.05 ± 20.96 with no statistically significant ($p=0.990$). By week 4, the stratum corneum removed was higher on the TXA side at 48.35 ± 13.66 compared to the placebo side at 44.51 ± 9.47 , resulting in a mean difference of 3.84 ± 17.19 , which was not statistically significant ($p=0.231$). The within-group mean differences from week 0 to week 4 were 1.85 ± 14.49 for the TXA group ($p=0.442$) and -1.94 ± 10.45 for the placebo group ($p=0.378$), indicating no significant changes within either group. The results showed that after the treatment, the 15% TXA tended to collect more stratum corneum than its baseline and the placebo, indicating a potential peeling effect. The information is provided in Figure 4.1 and Table 4.21.

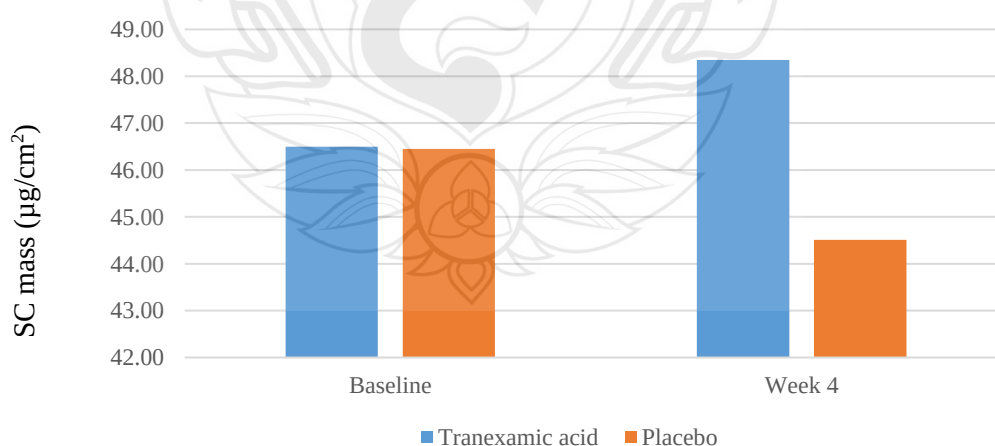


Figure 4.1 Mass ($\mu\text{g}/\text{cm}^2$, mean $\pm$ SD) of Stratum Corneum Removed After 10 Tape Strips under the Chin on the TXA and Placebo Parts at Baseline and Week 4

Table 4.21 Comparison of Stratum Corneum Mass Removed Under the Chin Between and Within 15% Tranexamic Acid and Placebo Groups at Baseline and Week 4 (n=3)

Time	15% Tranexamic acid	Placebo	Mean difference	p-value*
	Mean $\pm$ SD	Mean $\pm$ SD		
Week 0	46.49 $\pm$ 15.14	46.45 $\pm$ 9.45	0.05 $\pm$ 20.96	0.990
Week 4	48.35 $\pm$ 13.66	44.51 $\pm$ 9.47	3.84 $\pm$ 17.19	0.231
Mean difference	1.85 $\pm$ 14.49	-1.94 $\pm$ 10.45		
P-value**	0.442	0.378		

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

4.12 Submental Transepidermal Water Loss (TEWL)

The TEWL was measured under the chin areas at the location where pre- and post-stratum corneum (SC) removal was performed at baseline and week 4 between the 15% TXA and the placebo groups. At Week 0, both groups had similar mean scores of TEWL before the SC removal, with 10.50 $\pm$ 2.91 for the TXA and 10.58 $\pm$ 3.80 for the placebo with a negligible mean difference of -0.08 $\pm$ 4.35 and p-value 0.977. After the SC removal, the mean scores increased to 13.80 $\pm$ 5.04 for the TXA and 14.95 $\pm$ 7.02 for the placebo, resulting in a mean difference of -1.15 $\pm$ 8.62 (p = 0.839). Within-group mean differences of TEWL for the TXA were 3.30 $\pm$ 2.59 (p=0.158) and 4.37 $\pm$ 3.39 for the placebo (p=0.156), indicating no significant changes within either group. At Week 4, before the SC removal, the mean scores of TEWL were 11.47 $\pm$ 0.75 for the TXA and 11.50 $\pm$ 1.68 for the placebo, with a negligible mean difference of -0.03 $\pm$ 1.01 (p=0.960). After the SC removal, the mean scores dramatically increased to 24.47 $\pm$ 5.50 for the TXA and 13.73 $\pm$ 4.05 for the placebo, resulting in a mean difference of TEWL of 10.73 $\pm$ 9.49, which was not statistically significant (p=0.189). Within-group mean differences of TEWL for the TXA were 13.00 $\pm$ 5.88 (p=0.062) and 2.23 $\pm$ 2.71 for the placebo (p=0.290), showing a dramatic increase in the TXA group but not in the placebo group. The information is demonstrated in Table 4.22.

Table 4.22 Comparison of Transepidermal Water Loss (TEWL) and Mean Differences Between and Within 15% Tranexamic Acid and Placebo Groups at Baseline and Week 4, Before and After Removal of Stratum Corneum Under the Chin (n=3)

Time	15% Tranexamic acid	Placebo	Mean difference	p-value*
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Week 0				
Before	10.50 $\pm$ 2.91	10.58 $\pm$ 3.80	-0.08 $\pm$ 4.35	0.977
After	13.80 $\pm$ 5.04	14.95 $\pm$ 7.02	-1.15 $\pm$ 8.62	0.839
Mean difference	3.30 $\pm$ 2.59	4.37 $\pm$ 3.39		
P-value**	0.158	0.156		
Week 4				
Before	11.47 $\pm$ 0.75	11.50 $\pm$ 1.68	-0.03 $\pm$ 1.01	0.960
After	24.47 $\pm$ 5.50	13.73 $\pm$ 4.05	10.73 $\pm$ 9.49	0.189
Mean difference	13.00 $\pm$ 5.88	2.23 $\pm$ 2.71		
P-value**	0.062	0.290		

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

Transepidermal water loss (TEWL) and mean difference between 15% TXA and placebo were assessed at baseline and week 4 before and after removing the stratum corneum under the chin. Before the SC removal, the TXA group exhibited a mean TEWL of 10.50 $\pm$ 2.90 at week 0 and 11.47 $\pm$ 0.75 at week 4, resulting in a mean difference of -0.97 $\pm$ 2.62 (p=0.589). The placebo group showed a mean TEWL of 10.58 $\pm$ 3.80 at week 0 and 11.50 $\pm$ 1.68 at week 4 with a mean difference of -0.93 $\pm$ 2.12 (p=0.532). Within-group comparisons indicated a mean difference of 0.08 $\pm$ 4.35 at week 0 (p=0.997) and 0.03 $\pm$ 1.01 at week 4 (p=0.960). After the SC removal, the TXA group exhibited an increase in mean TEWL from 13.80 $\pm$ 5.04 at week 0 to 24.47 $\pm$ 5.50 at week 4, with a significant mean difference of -10.67 $\pm$ 3.11 (p=0.027). In contrast, the placebo group had a mean TEWL of 14.95 $\pm$ 7.02 at week 0 and 13.73 $\pm$ 4.05 at week 4, with a mean difference of 1.22 $\pm$ 4.91

($p=0.709$). Within-group comparisons showed mean differences of 1.15 ± 8.62 at week 0 ($p=0.839$) and -10.73 ± 9.49 at week 4 ($p=0.189$). These findings are detailed in Table 4.23.

Table 4.23 Comparison of Transepidermal Water Loss (TEWL) and Mean Differences Between and Within 15% Tranexamic Acid and Placebo Groups at Baseline and Week 4, Before and After Stratum Corneum Removal (n=3)

Time	Week 0	Week 4	Mean difference	p-value*
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Before				
15% Tranexamic acid	10.50 ± 2.90	11.47 ± 0.75	-0.97 ± 2.62	0.589
Placebo	10.58 ± 3.80	11.50 ± 1.68	-0.93 ± 2.12	0.532
Mean difference	0.08 ± 4.35	0.03 ± 1.01		
P-value**	0.977	0.960		
After				
15% Tranexamic acid	13.80 ± 5.04	24.47 ± 5.50	-10.67 ± 3.11	0.027
Placebo	14.95 ± 7.02	13.73 ± 4.05	1.22 ± 4.91	0.709
Mean difference	1.15 ± 8.62	-10.73 ± 9.49		
P-value**	0.839	0.189		

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

4.13 Comparison of Periorbital Wrinkle Scores Between Tranexamic Acid and Placebo Treatments

The study assessed the efficacy of 15% TXA and placebo in improving periorbital wrinkles, comparing outcomes both between and within the groups over eight weeks. Overall, the TXA group exhibited a more substantial reduction in periorbital fine lines compared to the placebo group. Nonetheless, there were no statistically significant

differences in wrinkle reduction between the two groups at any point during the study ($p=0.05$). Within-group analysis revealed no significant improvement in fine lines for the placebo group, whereas a marked reduction was observed in the TXA group ($p=0.007$).

Table 4.24 Comparison of Periorbital Wrinkle Scores Between and Within 15% Tranexamic Acid and Placebo Groups (n=15)

Time	15% Tranexamic acid			Placebo			p-value*
	Mean $\pm$ SD	Median (IQR)	Min-Max	Mean $\pm$ SD	Median (IQR)	Min-Max	
Baseline	21.93 $\pm$ 6.75	20.94 (17.82,25.09)	9.36-33.96	21.69 $\pm$ 6.72	20.44 (18.05,24.84)	10.34-34.83	0.318
Week 1	21.66 $\pm$ 6.69	20.41 (17.72,24.25)	9.37-33.52	21.67 $\pm$ 6.69	20.57 (18.63,24.34)	9.29-34.74	0.956
Week 2	21.17 $\pm$ 6.51	20.16 (17.13,23.81)	9.25-33.08	21.51 $\pm$ 6.68	20.35 (17.98,24.56)	9.54-34.61	0.202
Week 3	21.21 $\pm$ 6.02	19.76 (18.35,23.93)	10.54-32.63	21.48 $\pm$ 6.55	20.27 (17.79,24.17)	9.70-34.73	0.430
Week 4	21.20 $\pm$ 6.09	19.44 (18.22,23.68)	10.13-33.10	21.40 $\pm$ 6.60	19.67 (18.15,24.12)	9.80-34.78	0.591
Week 8	21.33 $\pm$ 6.14	20.75 (17.75,23.63)	9.03-32.54	21.43 $\pm$ 6.73	19.69 (17.98,24.48)	11.26-34.99	0.863
P-value**	0.007			0.501			

Note * signifies that the p-value between groups was calculated by Paired t-test

** signifies that the p-value within a group was calculated by Repeated measures ANOVA

The table below displays changes in periorbital wrinkle scores over time for subjects treated with 15% TXA, comparing baseline scores to those in subsequent weeks. Significant reductions in wrinkle scores were noted from baseline to week 1 ($p=0.020$), week 2 ($p<0.001$), week 3 ($p=0.029$), and week 4 ($p=0.020$), with no significant decrease observed at week 8 ($p=0.067$). A significant reduction was also seen from week 1 to week 2 ($p<0.001$), though no significant changes were found in other week-to-week comparisons. This data is detailed in Table 4.25.

Table 4.25 Mean Difference in Periorbital Wrinkle Scores Among Time with 15% Tranexamic Acid (n=15)

Comparisons among time	Mean difference of 15%Tranexamic acid	p-value*
Baseline – Week 1	-0.02 ± 0.59	0.020
Baseline – Week 2	-0.18 ±0.34	<0.001
Baseline – Week 3	-0.21 ±0.70	0.029
Baseline – Week 4	-0.28 ±0.78	0.020
Baseline – Week 8	-0.26 ±0.98	0.067
Week 1 – Week 2	-0.16 ±0.39	<0.001
Week 1 – Week 3	-0.19 ±0.62	0.138
Week 1 – Week 4	-0.27 ±0.63	0.096
Week 1 – Week 8	-0.25 ±1.01	0.259
Week 2 – Week 3	-0.03 ±0.54	0.851
Week 2 – Week 4	-0.11 ±0.65	0.895
Week 2 – Week 8	-0.09 ±0.97	0.512
Week 3 – Week 4	-0.08 ±0.43	0.875
Week 3 – Week 8	-0.06 ±0.95	0.687
Week 4 – Week 8	0.02 ±0.68	0.582

Note * signifies that the p-value was calculated by Paired t-test

4.14 Side Effects Evaluation

Subjects reported side effects in five categories: facial scaling, erythema, itching, burning, and stinging, as assessed through a questionnaire. No subjects experienced severe side effects. In the 15% TXA group, there was a progressive increase in mild scaling: one subject at week 2, three subjects at week 3, five subjects at week 4, and by week 8, no scales were reported. Two subjects reported mild erythema at week 2 and week 4, three subjects at week 3, and by week 8, no erythema was found. Moreover, two subjects reported an itching sensation in week 1, and three subjects reported itching in week 2; by week 3 through the end

of the study, no itching was reported. There were no reports of burning or stinging side effects. In contrast, in the placebo group, no reports of scaling and other possible side effects were noted throughout the study. According to the scaling score, mild scaling is defined as barely noticeable fine scales present in limited areas of the face. The information is demonstrated in Table 4.26.

Table 4.26 Side Effects Evaluated by the Subjects between 15% Tranexamic Acid and Placebo (n=15)

Side effect category	15% Tranexamic acid, n				Placebo, n			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Scales								
Week 1	15	-	-	-	15	-	-	-
Week 2	14	1	-	-	15	-	-	-
Week 3	12	3	-	-	15	-	-	-
Week 4	10	5	-	-	15	-	-	-
Week 8	15	-	-	-	15	-	-	-
Erythema								
Week 1	15	-	-	-	15	-	-	-
Week 2	13	2	-	-	15	-	-	-
Week 3	12	3	-	-	15	-	-	-
Week 4	13	2	-	-	15	-	-	-
Week 8	15	-	-	-	15	-	-	-
Itching								
Week 1	13	2	-	-	15	-	-	-
Week 2	12	3	-	-	15	-	-	-
Week 3	15	-	-	-	15	-	-	-
Week 4	15	-	-	-	15	-	-	-
Week 8	15	-	-	-	15	-	-	-
Burning								
Week 1	15	-	-	-	15	-	-	-
Week 2	15	-	-	-	15	-	-	-
Week 3	15	-	-	-	15	-	-	-
Week 4	15	-	-	-	15	-	-	-
Week 8	15	-	-	-	15	-	-	-

Table 4.26 (continued)

Side effect category	15% Tranexamic acid, n				Placebo, n			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Stinging								
Week 1	15	-	-	-	15	-	-	-
Week 2	15	-	-	-	15	-	-	-
Week 3	15	-	-	-	15	-	-	-
Week 4	15	-	-	-	15	-	-	-
Week 8	15	-	-	-	15	-	-	-

4.15 Satisfaction Evaluation

Satisfaction levels and mean scores for various skin conditions between the 15% TXA group and the placebo groups over multiple weeks were demonstrated in Table 4.33. Subjects in the 15% TXA group reported significantly greater satisfaction with the reduction in acne count and severity at week 3 ($p=0.019$) and week 4 ($p<0.001$) compared to the placebo group. Regarding the reduction in erythema, significant improvements were observed with TXA at week 1 ($p=0.019$), week 3 ($p=0.009$), and week 4 ($p<0.001$) compared to placebo.

The appearance of scales also showed significant improvement with TXA at weeks 2 ($p<0.001$), 3 ($p<0.001$), and 8 ($p=0.001$). In the week 8 satisfaction evaluation, subjects showed their impression as an overall treatment by the end of the study, not necessarily mean of the scale development in this week. However, there was no significant difference between the two groups in the reduction of periorbital fine lines at any time point ($p>0.05$). Overall, TXA demonstrated superior performance to placebo in reducing inflammatory acne and improving the appearance of scales, as demonstrated in Table 4.27.

Table 4.27 Global Patient Satisfaction Scale: Treatment between 15% Tranexamic Acid and Placebo (n=15)

Time	15% Tranexamic acid, n						Placebo, n				15% Tranexamic acid		p-value*
	Very unsatisfied	Unsatisfied	Neutral	Satisfied	Very Satisfied	Very unsatisfied	Unsatisfied	Neutral	Satisfied	Very Satisfied	Mean ± SD	Mean ± SD	
Reduction in Acne Count and Severity													
week 1	-	1	6	7	1	-	1	8	5	1	3.20 ± 1.01	3.40 ± 0.74	0.510
week 2	-	-	8	5	2	-	-	7	7	1	3.60 ± 0.74	3.60 ± 0.63	1.000
week 3	-	2	6	3	4	-	2	8	4	1	3.60 ± 1.06	3.27 ± 0.80	0.019
week 4	-	1	3	6	5	-	2	8	3	2	4.00 ± 0.93	3.33 ± 0.90	<0.001
week 8	-	1	7	6	1	-	1	8		2	3.47 ± 0.74	3.47 ± 0.83	1.000
Reduction in Erythema Effect													
week 1	-	2	5	8	-	-	-	-	-	-	3.40 ± 0.74	3.07 ± 0.59	0.019
week 2	-	2	8	5	-	-	2	10	3	-	3.20 ± 0.68	3.00 ± 0.76	0.082
week 3	-	1	8	5	1	4	4	7	4	-	3.40 ± 0.74	3.00 ± 0.76	0.009
week 4	-	1	2	8	4	4	4	7	4	-	4.00 ± 0.85	3.00 ± 0.76	<0.001
week 8	-	1	7	6	1	4	4	7	4	-	3.20 ± 0.86	3.07 ± 0.96	0.685
Appearance of Scales													
week 1	-	6	8	1	-	2	5	8	-	-	2.47 ± 0.64	2.40 ± 0.74	0.719
week 2	-	-	11	4	-	3	4	7	1	-	3.27 ± 0.46	2.40 ± 0.91	<0.001
week 3	-	-	8	6	1	1	6	7	1	-	3.53 ± 0.64	2.53 ± 0.74	<0.001
week 4	-	1	5	6	3	4	5	6	-	-	3.73 ± 0.88	3.33 ± 2.29	0.373
week 8	-	-	12	3	-	3	2	10	-	-	3.27 ± 0.46	2.47 ± 0.83	0.001

Table 4.27 (continued)

Time	15% Tranexamic acid, n						Placebo, n				15% Tranexamic acid		p-value*
	Very unsatisfied	Unsatisfied	Neutral	Satisfied	Very Satisfied	Very unsatisfied	Unsatisfied	Neutral	Satisfied	Very Satisfied	Mean ± SD	Mean ± SD	
Reduction in Periorbital Fine Lines													
week 1	-	-	7	7	1	-	-	7	7	1	3.60 ± 0.63	3.60 ± 0.63	1.000
week 2	-	-	9	5	1	-	-	9	5	1	3.47 ± 0.64	3.47 ± 0.64	1.000
week 3	-	-	7	7	1	-	-	7	7	1	3.33 ± 0.82	3.33 ± 0.82	1.000
week 4	-	1	9	2	3	-	1	9	2	3	3.47 ± 0.92	3.47 ± 0.92	1.000
week 8	-	3	9	1	2	-	-	9	1	2	3.13 ± 0.92	3.13 ± 0.92	1.000

Note * signifies that the p-value between groups was calculated by Paired t-test

The following summarizes the satisfaction ratings for a 15% TXA emulgel based on several properties: color, scent, texture, viscosity, absorption, and overall satisfaction. The emulgel received generally positive feedback, with the highest satisfaction scores for viscosity (2.80 ± 1.15), followed by absorption (2.47 ± 0.92) and color (2.47 ± 0.99). The lowest satisfaction was reported for texture (2.47 ± 1.30). These results suggest a moderately positive overall satisfaction among the respondents. The information is demonstrated in Table 4.28.

Table 4.28 Product Satisfaction of 15% Tranexamic Acid Emulgel (n=15)

Emulgel property	Level of satisfaction, n					Mean $\pm$ SD
	Very satisfied	Satisfied	Neutral	Unsatisfied	Very unsatisfied	
Color	3	4	6	2	-	2.47 ± 0.99
Scent	4	4	4	2	1	2.47 ± 1.25
Texture	4	4	5	-	2	2.47 ± 1.30
Viscosity	2	3	8	-	2	2.80 ± 1.15
Absorption	3	3	8	1	-	2.47 ± 0.92
Overall satisfaction	2	8	5	-	-	2.47 ± 1.36

4.16 Photos Analysis and Investigator Evaluation

Photos analysis included three areas:

1. Anti-inflammatory effect
2. Post-inflammatory hyperpigmentation and skin brightness
3. Desquamation formation

4.16.1 Anti-Inflammatory Effect

The overall reduction of facial redness caused by inflammatory acne (both active acne and post-inflammatory erythema acne) and other inflammatory lesions (e.g., rosacea and spider vein) were compared between 15% TXA and placebo at different time points.

The evaluation was done through photo analysis through VISIA® skin analysis, as shown in Figure 4.2. In the TXA group, there was a slight reduction in redness compared to the placebo group. Post-inflammatory erythema (PIE) showed gradual improvement over four weeks; by week 8, some PIE spots were significantly faded.

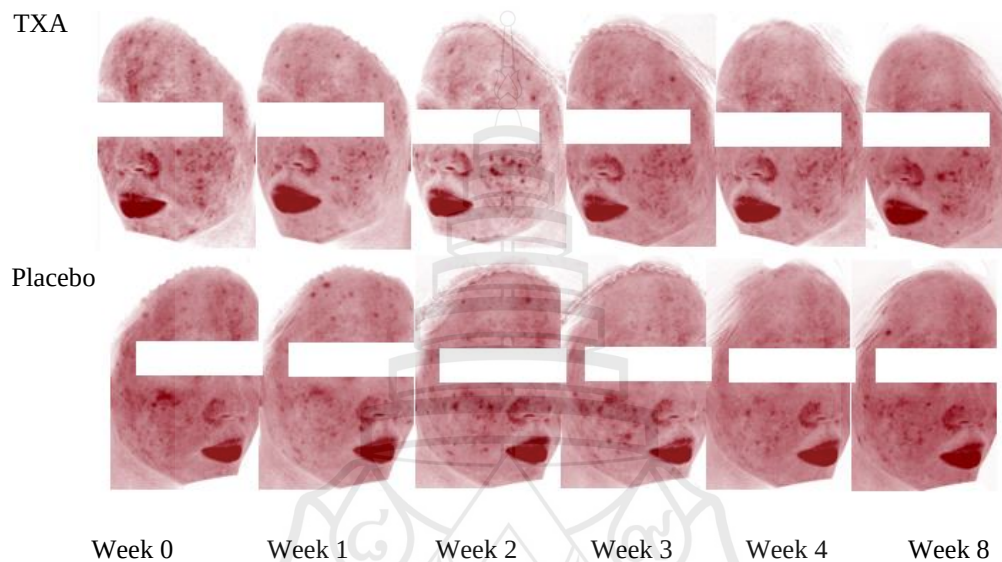


Figure 4.2 Red area Imaging from VISIA® Skin Analysis for the Tranexamic Acid-treated Side (Top) and the Placebo-treated Side (Bottom) at Baseline and at Weeks 1, 2, 3, 4, and 8 (from Left to Right)

4.16.2 Post-Inflammatory Hyperpigmentation and Skin Brightness

The overall changes in PIH acne and skin brightness were compared between the 15% TXA group and the placebo group at various time points. This evaluation was conducted using photo analysis through VISIA® Skin Analysis, as illustrated in Figure 4.3. Throughout the 8-week study, there was a gradual improvement in post-inflammatory hyperpigmentation (PIH) spots, with significant fading observed by the end of the period. The increase in skin brightness was more noticeable among participants with darker skin tones compared to those with fairer skin.

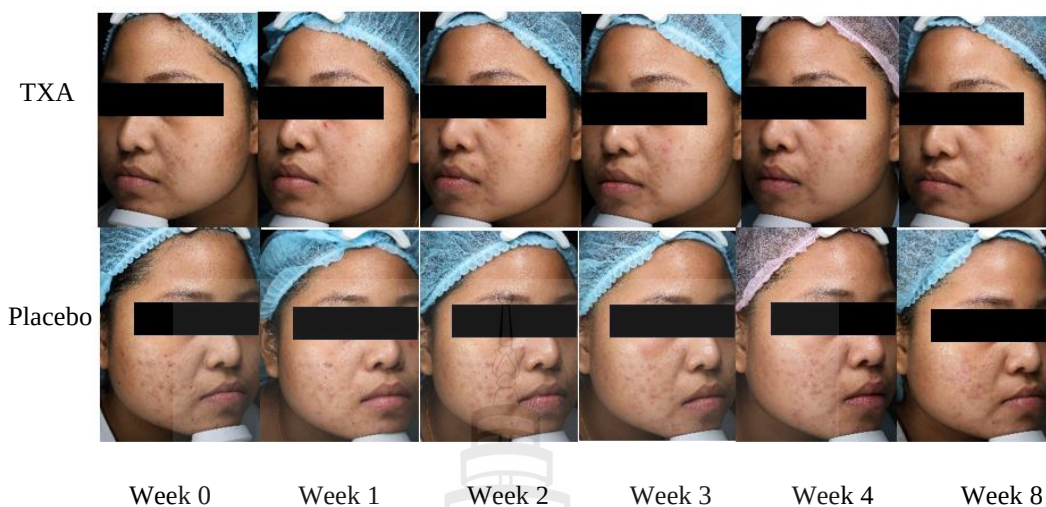


Figure 4.3 Imaging of PIH and Skin Brightness from VISIA® Skin Analysis for the Tranexamic Acid Side (Top) and the Placebo Side (Bottom) at Baseline and at Weeks 1, 2, 3, 4, and 8 (from Left to Right)

4.16.3 Desquamation Formation

Facial desquamation was monitored and compared between the 15% TXA group and the placebo group at various time points. This evaluation was conducted using photo analysis through VISIA® Skin Analysis, as illustrated in Figure 4.4. Following the application of TXA emulgel, the subject experienced skin dryness. A significant increase in mild desquamation was observed from weeks 3 onward in the TXA group compared to the placebo group. However, after changing the product from TXA to placebo, no scales were observed. Table 4.4 demonstrates the presence of fine scales localized at the jawline on the side treated with TXA. Notably, desquamation was not observed on the placebo-assigned side throughout the study period.

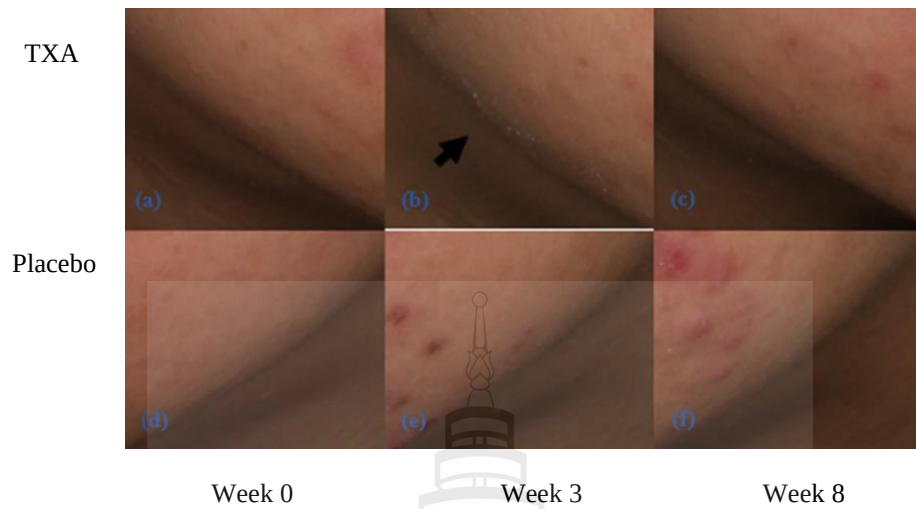


Figure 4.4 Imaging of Mild Desquamation from VISIA® Skin Analysis in a Participant. The Top Three Images Present Baseline (a), Week 3 (b), and Week 8 (c) in the 15% Tranexamic Acid Group. The Bottom Three Images Present Baseline (d), Week 3 (e), and Week 8 (f) in the Placebo Group (from Left to Right)

CHAPTER 5

DISCUSSION AND CONCLUSION

This research was designed as a randomized, double-blind, placebo-controlled, split-face trial. The primary objective was to assess the efficacy of topical 15% topical tranexamic acid (TXA) in treating mild to moderate inflammatory acne and its peeling effects, in comparison to a placebo over a period of 8 weeks. Additionally, the study evaluated the impact on TEWL, sebum, SC quantification, and submental TEWL, as well as the improvement of periorbital fine lines, side effects, and participant satisfaction with the treatment.

5.1 Discussion

5.1.1 Non-Inflammatory Acne Counts

The present study found significant differences in acne count reduction between the 15% TXA and placebo groups. Notable reductions in total non-inflammatory acne were observed starting from week 3 ($p=0.047$ onward), and in closed comedones at week 4 ($p=0.025$). Within the TXA group, significant changes were more pronounced in open comedones, with a significant reduction ($p=0.041$). These findings suggest that 15% TXA can potentially reduce non-inflammatory acne, regardless of subtype, starting from week 3 after treatment.

Regarding how TXA reduces non-inflammatory acne, Charoenwattanayothin et al. proposed that TXA might have an exfoliating effect on acne lesions, potentially contributing to the reduction of non-inflammatory acne. In line with this perspective, we suggest that TXA may exert a comedolytic effect by peeling off the thick overlay of keratocytes and removing dead cells, including sebum, from the follicular opening. This process helps eliminate microcomedones beneath the skin and enhances non-inflammatory acne treatment (Alikhan & Maibach, 2014). However, their earlier research found that a 10% topical TXA gel did not

significantly decrease the number of non-inflammatory acne lesions (Charoenwattanayothin et al., 2022).

5.1.2 Inflammatory Acne Counts

The present study showed that 15% of TXA significantly reduced total inflammatory acne counts at week 2 ($p=0.005$) and papule counts from week 2 ($p=0.019$) onward compared to the placebo group. The two groups had no significant differences regarding other forms of inflammatory acne. The study suggests that, while both groups experienced increased acne numbers during the trial, the 15% TXA effectively treats inflammatory acne starting from week 2 after the treatment.

The study result is aligned with the previous study on 10% TXA, which showed a significant reduction in total inflammatory acne starting at week 4 ($p=0.012$). A notable difference, however, is that there was a significant decrease in the counts of papules and pustules beginning at week 4 ($p=0.027$), as reported by Charoenwattanayothin et al. (2022).

Moreover, within this study, we tried to investigate the potential factors contributing to the increase in acne prevalence among participants. The top three factors include (I.) the influence of the menstrual cycle, (II.) acne flares associated with the use of TXA, and (III.) the impact of wearing facial masks. Since all the subjects were female, the menstrual cycle was the most significant uncontrollable factor contributing to acne exacerbation. Women tend to experience a higher incidence of acne flare during the pre-menstrual period (Lucky, 2004; Stolla et al., 2001) due to the fluctuation of sex hormones. During the follicular and periovulatory phases, levels of androgens and estrogens are elevated, while progesterone levels are diminished. These hormonal shifts are thought to contribute to an escalation in sebum production and an augmentation of skin microflora (Raghunath et al., 2015; Stephens, 1997; Steventon, 2011). Subjects experienced their pre-menstrual period at various times during the study, with one subject experiencing acne flare during the pre-menstrual, perimenstrual, and post-menstrual periods. Next, a significant number of participants reported acne breakouts after applying the TXA emulgel on the face. This breakout involved comedones, unerupted acne beneath the skin, and papule-form post-acne scars. This reaction is reminiscent of the 'retinoid purge/uglies,' suggesting that the TXA may function similarly to topical retinoids. The primary cause of acne flare-ups is the increased cell

turnover induced by an agent, which in this case is TXA (Hobkirk, 2022). The exfoliative effect induced by the cell turnover process causes the outermost skin layer (stratum corneum) to shed, removing the keratotic plugs from comedones and enhancing cell regeneration. The cell turnover rate is accelerated beyond the normal physiological rate by the TXA, resulting in skin and pre-existing acne irritation. The irritation and exfoliative effect both stimulate the pre-existing acne, causing it to inflame and emerge on the skin surface simultaneously, leading to an acne breakout (Mukherjee et al., 2006; Sayer, 2023). In addition, Alikhan and Maibach (2014) proposed that acne flare-ups are due to follicular inflammatory factors released after applying the medication. However, there was a contrary theory that the medication did not induce acne flare but resulted from a natural progression of acne disease (Del Rosso & Tretinoin, 2008; Yentzer et al., 2009). The third factor that caused acne exacerbation was the prolonged use of facial masks. “Maskne,” or acne exacerbated by mask-wearing, was a significant factor, especially during the COVID-19 pandemic. The prolonged use of facial masks led to heat, humidity, and pH changes, resulting in mechanical stress, microbiome dysbiosis, and follicular occlusion (Teo, 2021). Subjects complained that the heat and moisture trapped inside the mask caused acne breakouts. Additionally, two subjects reported allergic reactions to the mask.

5.1.3 Severity of Acne

5.1.3.1 The Grade of Acne Severity

The grade of acne severity was assessed over the 8-week study period. Although the acne severity in the TXA group was lower than in the placebo group throughout the study, there was no significant difference ($p > 0.05$) between the two groups. This study suggests that the 15% TXA results in a slight reduction in acne severity compared to the placebo. This study diverges from prior research on 10% TXA, which reported significant differences at weeks 6 and 8, each with a p-value of 0.01. The lack of significant differences in acne severity reduction between the two groups in our study can be attributed to two main factors: (I.) an initial acne flare-up during the first four weeks and (II.) the switch from a 15% TXA product to a placebo at week 4. Consequently, the acne severity results observed at week 8 indicate the remaining effects of TXA one month after its discontinuation.

5.1.3.2 Erythema Reduction in Inflammatory Acne

The study found that 15% TAX effectively reduces the erythematous phase of the inflammatory papules since week 2 ($p=0.019$). The reduction of the inflammatory process by the TXA is due to the inhibition of serine protease (SP) activity, preventing the activation of PAR-2 and decreasing the production of active forms of LL-37. Consequently, it suppresses inflammation, reduces erythema, and improves the epidermal permeability barrier function of damaged skin (Zhong et al., 2015). Furthermore, TXA attenuates the expression of TLR-2, KLK5, and Camp; decreases the production of proinflammatory cytokines IL-6 and TNF α ; reduces neutrophil and Th17 chemokine (CCL10) expression; and suppresses angiogenesis. All of these result in a reduction of inflammation and erythema (Li et al., 2019).

In addition to its anti-inflammatory properties, TXA has demonstrated antimicrobial effects, which is a crucial discovery given that *C. acnes* triggers the inflammatory cascade in inflammatory acne. It was found that TXA at a concentration of 10 mg/mL significantly reduced *C. acnes* by 69.9% in an in vitro planktonic model (Benjumea et al., 2022). Although the precise antibacterial mechanism of TXA has not been fully elucidated, it is hypothesized that TXA exerts both direct and indirect antibiotic effects on pathogen growth. It was found that TXA inhibits bacterial biofilm formation by blocking bacterial lysine uptake (Lohinai et al., 2015). Additionally, TXA can prevent bacterial aggregation and inhibit bacterial growth at higher concentrations (Zhang et al., 2021). Moreover, TXA may enhance the immune response by inhibiting the conversion of plasminogen to plasmin, which induces an immunosuppressive response, thereby reducing infection (Draxler et al., 2019).

5.1.4 Desquamation Index

On the side treated with the 15%TXA, the desquamation index steadily increased during the first four weeks. The significant differences in the desquamation index between the two groups were observed from week 3 ($p=0.035$) onward. In contrast, on the placebo side, the desquamation index decreased over the subsequent weeks with no significant difference ($p>0.05$). By week 8, after the TXA group switched the product to placebo since week 4, the desquamation index of both groups was nearly identical, with no significant difference ($p>0.05$). The study indicates that 15% of TXA induces skin desquamation since week 3.

Clinically, 60% of the subjects (9 out of 15) reported experiencing skin desquamation. Of these, three subjects observed the development of fine scales in specific facial areas, including the jawline, around the corners of the mouth, and peri-inflammatory acne papules/nodules. The remaining participants initially did not notice the peeling effect during the day, as they found no significant differences between the TXA-treated side and the placebo side, except for the skin dryness. However, they began to detect the peeling during their routine facial washing and while applying the emulgel, as rubbing their fingers against their face led to the removal of the outer skin layer in the form of 'scurf' during the third and fourth week

The relationship between the indicative desquamation index and the level of skin shedding was also supported by the study of quantitative measurement of desquamation and skin elasticity in diabetic patients conducted by Yoon et. al. They found that those diabetic patients who suffered from skin xerosis and peeling had greater mean desquamation index number of 116.5 ± 10.9 as compared to the non-diabetic individuals (control group) with a mean desquamation index number of 114.7 ± 27.6 , although there was no statistically significant (Yoon et al., 2002). On the other hand, a study of new cosmetic formulations for treating mild to moderate infantile atopic dermatitis demonstrated the relationship between the desquamation index and skincare products like moisturizers and emollients and a reduced occurrence of skin shedding. They found that the mean desquamation index reduced by 30.95% at 14 days and 21% at 28 days from baseline after applying the formula product (de Lucas et al., 2019). These studies suggest that skin with an exfoliative condition exhibits a higher desquamation index compared to healthier skin, which demonstrates a lower desquamation index.

5.1.5 Transepidermal Water Loss (TEWL)

Subjects treated with 15% TXA exhibited an increase in TEWL during the first four weeks of the study. Conversely, the TEWL in the placebo group showed a consistent decrease. Significant differences in TEWL between the two groups were observed from week 3 ($p=0.013$) onward. Notably, by week 8, after switching the product to a placebo, the TEWL significantly decreases from week 4 to week 8 ($p=0.009$) in the TXA group. This study indicates that a prominent change in TEWL begins at week 3 after applying 15% of TXA emulgel.

An increase in TEWL levels following the application of the TXA suggests a temporary disturbance in the barrier function as evidenced by a progressive increase in TEWL during treatment and subsequently returns to its baseline upon switching to a placebo. So, in this study, we hypothesize that 15% of TXA causes water/skin barrier dysfunction to a certain degree. Contrarily, our hypothesis is inconsistent with prior research, which demonstrated that TXA enhances skin integrity and restores the cutaneous barrier function. According to Yuan et al., they found that TXA significantly speeded up the barrier restoration and increased the amount of occludin transmembrane protein in tight junctions, therefore improving the skin barrier function (Yuan et al., 2014). Similarly to the study conducted by Tohgasaki et al., they found that TXA effectively reversed the skin barrier dysfunction by mitigating the reduction of claudin-4, E-cadherin, and occludin levels, which were adversely affected by ENO1 overexpression. Furthermore, TXA preserved the integrity of tight junctions by preventing the degradation of the extracellular matrix and tight junction proteins (Tohgasaki et al., 2018). Furthermore, Katsuta et al. revealed that t-AMCHA methylamide (tranexamic acid) contributed to the acceleration of barrier recovery (Katsuta et al., 2005).

Previous studies have used topical TXA at concentrations below 5% on deteriorated skin. As a result, they primarily observed the therapeutic effects of TXA. Contrary to this study, we increased the concentration of TXA to 15% and observed skin dryness and desquamation. The findings are supported by previous studies where raising the concentration of TXA to 10% caused greater skin dryness and led to the appearance of fine scales in patients (Charoenwattanayothin et al., 2022; Jakhar et al., 2020). Therefore, higher concentrations of TXA may disrupt the intercellular cohesion of the stratum corneum layer, impair barrier function, and reduce skin integrity, as evidenced by the higher desquamation index coupled with elevated transepidermal water loss (TEWL). These effects are expected to normalize once the product is discontinued.

5.1.6 Sebum Levels

The results showed a consistent reduction in sebum levels for both the 15% TXA group and the placebo group throughout the study. However, the reduction was more pronounced in the TXA group. Significant differences in sebum level reduction between the two groups were observed from week 2 ($p=0.039$) onward. This study suggests that TXA

significantly reduces sebum levels since week 2. The severity of skin dryness increased over the subsequent weeks.

The precise mechanism by which TXA reduces sebum production remains unknown. However, we hypothesized that the exfoliative/comedolytic effect of TXA not only removes sebum in the follicle but may also concurrently strip away excess facial oil. Nonetheless, the current understanding of acne pathogenesis and anti-acne agents reveals only a few factors that stimulate sebum production or overproduction. Androgens, for instance, stimulate lipid synthesis through the PI3K/Akt pathway. Insulin and IGF-1 promote lipid synthesis by increasing SREBP-1 expression via the PI3K/Akt/FoxO1/mTORC1 and MAPK pathways. Additional stimulators of sebum synthesis include CRH, α MSH, and substance P (Cong et al., 2019). TXA might influence the reduction of sebum production by inhibiting one of these mechanisms.

5.1.7 Stratum Corneum Quantification

In the 15% TXA group, the mean stratum corneum (SC) mass increased from $46.49 \pm 15.14 \mu\text{g}/\text{cm}^2$ at baseline to $48.35 \pm 13.66 \mu\text{g}/\text{cm}^2$ at week 4, though this increase was not statistically significant ($p=0.442$). Furthermore, at week 4, the mean stratum corneum mass in the TXA group was higher than the placebo group at $44.51 \pm 9.47 \mu\text{g}/\text{cm}^2$; nonetheless, there was no significant difference between these groups ($p=0.231$). The study suggests 15% TXA causes a greater amount of stratum corneum to be removed by tape stripping compared to placebo and untreated areas (baseline).

Submental Transepidermal Water Loss (TEWL) was measured at baseline and at week 4 following the removal of the stratum corneum (SC) to assess the impact of TXA on skin integrity compared to a placebo. In the TXA group, there was a significant increase in TEWL after tape stripping, from baseline (13.80 ± 5.04) to week 4 (24.47 ± 5.50), with a p -value of 0.027. This study suggests that TXA causes significant changes in TEWL.

Both SC's protein quantification and submental TEWL measurements indicate that 15% TXA disrupts the cohesion force between intercorneocytes and disturbs the water barrier function. This disruption leads to increased superficial cutaneous detachment. These two parameters are crucial in determining the strength of skin integrity. According to Alexander et al., when skin integrity is compromised due to weakened intercellular cohesion and a

disrupted barrier function, more corneocytes are removed by the tape, leading to higher levels of transepidermal water loss (Alexander et al., 2018).

Our study's results are consistent with those of Bashir et al., who found that 2% salicylic acid (SA) generated more stratum corneum (SC) protein through the tape-stripping process compared to vehicle-treated and control sites. Additionally, they observed a significant increase in transepidermal water loss (TEWL) following treatment with 2% SA, as opposed to the vehicle and control sites (Bashir et al., 2005). Similarly, the study by Waller et al. demonstrated that keratolytic agents such as benzoyl peroxide (BP), retinoic acid (RA), and salicylic acid (SA) produced more SC protein through the tape stripping process than untreated and control sites, with varying results (Waller et al., 2006).

5.1.8 Wrinkle Assessment

There was a significant reduction in wrinkle scores within the 15% TXA group ($p=0.007$), and the mean difference from week 1 to baseline ($p=0.020$) onward was also significantly reduced. The study indicates that 15% TXA could reduce periorbital wrinkles.

The anti-wrinkle effect of TXA was supported by a study conducted by Hiramoto et al. They found that TXA alleviated wrinkles by reducing mast cell proliferation and enhancing fibroblast proliferation (Hiramoto et al., 2016). Additionally, they observed that wrinkle reduction was more pronounced in females than in males, attributing this difference to the role of β -endorphin produced by macrophages (Hiramoto et al., 2016).

5.1.9 Side Effects

In the 15% TXA group, out of 15 participants, two experienced mild erythema at both week 2 and week 4, and three experienced it at week 3. Additionally, two subjects reported itching at week 1, and three subjects experienced itching at week 2. All these side effects were minimal and resolved spontaneously without additional treatment. No other side effects, such as burning or stinging, were observed during the course of the study. The study indicates that 15% TXA could cause mild and tolerable side effects such as erythema and itching. The findings are consistent with the previous studies on topical TXA treatment for inflammatory skin conditions such as acne and rosacea, which reported minor side effects, including erythema, scaling, and pruritis (Charoenwattanayothin et al., 2022; Daadaa et al., 2021; Sobhan et al., 2023). The molecular structure of TXA includes a monocarboxylic acid

group (-COOH). This free carboxylic acid group has been identified as the reason for generating these side effects (Mukherjee et al., 2006).

5.1.10 Subjects' Satisfaction

Participants reported satisfaction with the reduction in the number and severity of acne starting from week 3 ($p=0.019$) onwards after using the 15% TXA emulgel compared to the placebo. They also expressed satisfaction with the reduction in acne erythema starting from week 1 ($p=0.019$). Some participants began to notice skin desquamation starting at week 2 ($p<0.001$). However, none of the subjects were satisfied with the reduction of periorbital fine lines in the treated area. Overall, TXA performed superior to placebo in reducing inflammatory acne and inducing skin desquamation.

5.1.11 Physicians' Evaluation and Photo Analysis

The photo evaluation encompasses three aspects: the reduction of facial redness or anti-inflammatory effect, the reduction of post-inflammatory hyperpigmentation (PIH) from acne scars and skin brightening effect, and the occurrence of desquamation. In the TXA group, there was a slight reduction in redness compared to the placebo group. Post-inflammatory erythema (PIE) of acne scars showed gradual improvement over four weeks, but by week 8, those PIE acnes had significantly faded. Post-inflammatory hyperpigmentation (PIH) from acne scars showed gradual improvement during the 4 weeks of the study, with significant fading observed by the end of the study. The increase in skin brightness was more noticeable among participants with darker skin tones compared to those with fairer skin. The 15% TXA treatment induces skin desquamation starting from week 3 of the study.

TXA treatment, which improves skin inflammation, was studied in inflammatory acne, PIE acne, and rosacea skin diseases. (Bazargan et al., 2023; Charoenwattanayothin et al., 2022; Zhong et al., 2015). Several studies supported the reduction of PIH acne and increase in skin brightness with TXA (da Silva Souza et al., 2021; Ebrahimi & Naeini, 2014; Kaikati et al., 2023; Sobhan et al., 2023). Treatment with topical TXA showed a report of skin desquamation (Charoenwattanayothin et al., 2022; Ebrahimi & Naeini, 2014).

Tranexamic acid has emerged as a promising therapeutic alternative for acne vulgaris, demonstrating efficacy comparable to that of retinoic acid. Its multifaceted mechanism of action encompasses anti-inflammatory, keratolytic, anti-comedogenic, and

antimicrobial properties. Additionally, TXA can modulate sebum production, inhibit melanogenesis, reduce erythema, and promote skin rejuvenation through mild chemical peeling effects. Notably, TXA presents a more favorable side effect profile than retinoic acid, with most patients experiencing only mild and tolerable adverse reactions. Furthermore, the absence of teratogenic potential in TXA confers a significant advantage in terms of safety, particularly for patients of reproductive age.

5.2 Conclusion

The 15% tranexamic acid (TXA) emulgel effectively treats both inflammatory and non-inflammatory acne through its anti-inflammatory, sebum-reducing, antimicrobial, and keratolytic effects. Noticeable improvements were observed from week 2 for inflammatory acne and from week 3 for non-inflammatory acne. Among inflammatory acne subtypes, papules show a particularly favorable response, while both closed and open comedones respond well among non-inflammatory subtypes. The treatment also accelerated the resolution of inflammatory papules from week 2 compared to placebo, contributing to reduced erythema.

The 15% TXA emulgel effectively induces skin peeling beginning in week 3. This peeling is generally mild and barely perceptible in some cases. Studies on transepidermal water loss (TEWL), sebum levels, and stratum corneum integrity assessed by protein assay all corroborate the occurrence of skin desquamation. This desquamation enhances skin rejuvenation, evidenced by significant reductions in periorbital fine lines observed as early as week 2 compared to baseline.

Furthermore, TXA aids in blemish reduction by alleviating post-inflammatory erythema (PIE) and post-inflammatory hyperpigmentation (PIH) associated with acne scars while also lightening overall skin tone. Despite mild and tolerable side effects such as erythema and itching, which lasted 1 to 2 weeks and resolved spontaneously without intervention, subjects expressed satisfaction with the acne treatment and were impressed by the rejuvenating effects following skin peeling.

5.3 Suggestions

Tranexamic acid (TXA) at a 15% concentration presents a promising alternative for treating acne vulgaris, demonstrating comprehensive efficacy across all known pathogenic mechanisms. The current study provides evidence of TXA's capacity to ameliorate acne vulgaris symptoms. In addition to its anti-acne properties, TXA offers rejuvenating effects by promoting superficial exfoliation, thereby diminishing periorbital fine lines and attenuating skin discoloration, including erythema and hyperpigmentation. Furthermore, TXA exhibits a favorable safety profile, with minimal and tolerable adverse effects and no known teratogenic potential.

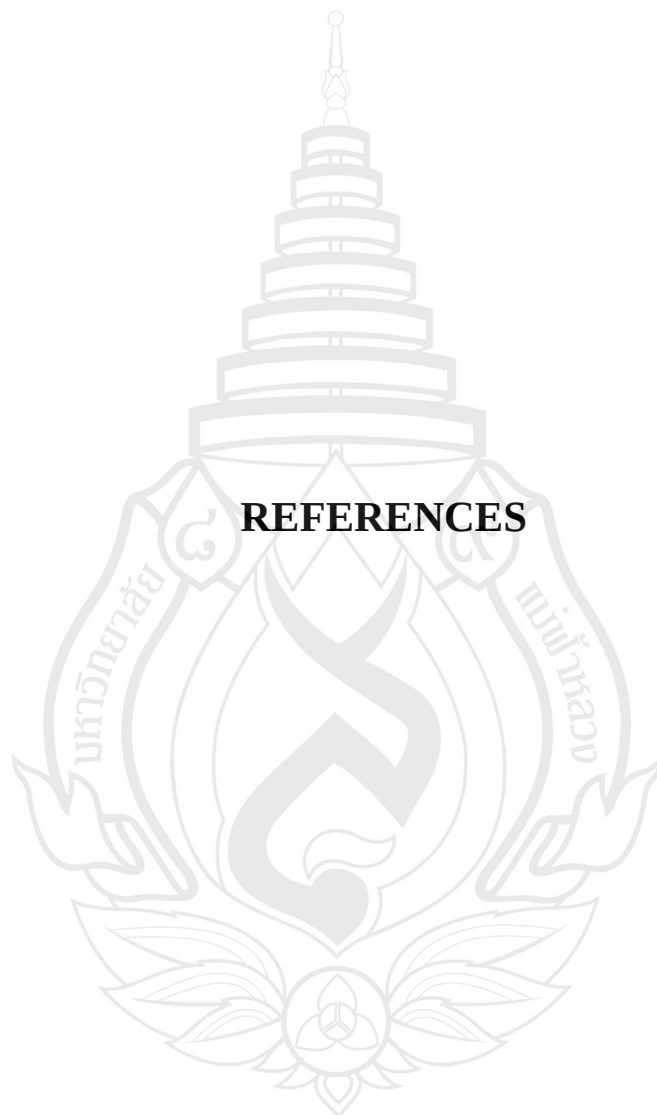
5.3.1 Further studies are needed to evaluate the antibiotic effect of TXA on *C. acnes*, utilizing additional parameters such as Wood's lamp examination and porphyrin measurements.

5.3.2 Further scientific studies are required to explore the specific mechanism of desquamation associated with TXA.

5.3.3 Further scientific studies are necessary to investigate how TXA reduces sebum production.

5.3.4 Further studies are needed to compare the efficacy of TXA in treating acne with other agents, including topical retinoids and benzoyl peroxide.

5.3.5 In this study, we identified an uncontrollable factor affecting the clinical observation of scale formation. Participants' routine facial washing and product application, which involved rubbing the face, caused the outer skin surface to slough off before they met with the investigator for evaluation.



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APPENDICES

APPENDIX A

ETHICAL APPROVAL DOCUMENT



The Mae Fah Luang University Ethics Committee on Human Research
333 Moo 1, Tha Sad, Muang, Chiang Rai 57100
Tel: (053) 917-170 to 71 Fax: (053) 917-170 E-mail: rechuman@mfl.ac.th

CERTIFICATE OF APPROVAL

COA: 098/2022 Protocol No: EC 22001-20

Title: The peeling effect of topical 15% Tranexamic acid in inflammatory acne

Principal Investigator: Chawalee Chueachavalit, M.D.

School: Anti-aging and Regenerative Medicine

Funding support: Personal Funds

Approval:

1) Research protocol	Version 3 date June 8, 2022
2) Information sheet for research project participants	Version 3 date June 8, 2022
3) Informed consent form	Version 1 date January 5, 2022
4) Case Record Form, Questionnaire and Assessment Form	Version 3 date June 8, 2022
5) Instruction for participants	Version 3 date June 8, 2022
6) Research participant recruitment information	Version 3 date June 8, 2022
7) Principal investigator and Co-investigators	
- Chawalee Chueachavalit, M.D.	

The aforementioned documents have been reviewed and approved by the Mae Fah Luang University Ethics Committee on Human Research in compliance with international guidelines such as Declaration of Helsinki, the Belmont Report, CIOMS Guidelines and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice (ICH - GCP)

Date of Approval: June 21, 2022

Date of Expiration: June 20, 2023

Frequency of Continuing Review: 1 Year



(Assoc. Prof., Maj. Gen. Sangkai Chaminvanakij, M.D.)
Chairperson of the Mae Fah Luang Ethics Committee on Human Research

APPENDIX B

INFORMATION SHEET

เอกสารชี้แจงข้อมูลแก่อาสาสมัครที่เข้าร่วมในโครงการวิจัย

(Research Subject Information Sheet)

ชื่อโครงการวิจัย: การศึกษาผลของการลอกผิวจากกรดทรานเอกซามิค 15% ในการรักษาสิวอักเสบ

ผู้วิจัยหลัก : แพทย์หญิงชวลี เชื้อขวลิต สำนักวิชาเวชศาสตร์ชะลอวัยและฟื้นฟูสุขภาพ มหาวิทยาลัยแม่ฟ้าหลวง

ชื่ออาจารย์ที่ปรึกษา : อาจารย์ ดร. แพทย์หญิง สิริทิพย์ ชัยชโลทรกุล สำนักวิชาเวชศาสตร์ชะลอวัยและฟื้นฟูสุขภาพมหาวิทยาลัยแม่ฟ้าหลวง, ผู้ช่วยศาสตราจารย์ ดร. ทวี สายวิชัย คณะสาธารณสุขศาสตร์มหาวิทยาลัยมหิดล และ อาจารย์ ดร. พริยา เอกจริยาวัฒน์ คณะสาธารณสุขศาสตร์ มหาวิทยาลัยมหิดล

ผู้สนับสนุนทุนวิจัย : ไม่มี

ท่านได้รับการเชิญชวนให้เข้าร่วมโครงการวิจัยนี้ เนื่องจากท่านได้รับการวินิจฉัยเป็นโรคผิวหนังอักเสบระดับน้อยถึงปานกลาง ก่อนที่ท่านจะตกลงใจเข้าร่วมหรือไม่ โปรดอ่านข้อความในเอกสารนี้อย่างถี่ถ้วน เพื่อให้ทราบถึงเหตุผลและรายละเอียดของโครงการวิจัยนี้ว่า หากเข้าร่วม ท่านจะต้องทำอะไรบ้าง รวมทั้งข้อดีและข้อเสียที่อาจเกิดขึ้นในระหว่างการทำวิจัย

หากท่านมีข้อสงสัยใด ๆ กรุณาซักถามจากทีมงานผู้วิจัย ซึ่งจะเป็นผู้ตอบคำถามจนกว่าท่านจะเข้าใจอย่างชัดเจน ท่านสามารถปรึกษาญาติพี่น้อง เพื่อนหรือแพทย์ที่ท่านรู้จัก ก่อนตัดสินใจว่าจะเข้าร่วมหรือไม่เข้าร่วมในโครงการวิจัยนี้

การเข้าร่วมในโครงการวิจัย จะต้องเป็น **ความสมัครใจ** ของท่าน ไม่มีการบังคับหรือชักจูง ถ้าท่านตัดสินใจเข้าร่วม กรุณาลงนามในเอกสารแสดงเจตนายินยอมเข้าร่วมโครงการวิจัยนี้

เหตุผลความเป็นมา และวัตถุประสงค์ของโครงการวิจัย

สิวเป็นโรคผิวหนังอักเสบเรื้อรังที่มีผลต่อหน่วยชนและต่อมไขมัน มักพบที่บริเวณ ใบหน้า ลำคอ และช่วงบนของลำตัว ช่วงอายุที่มักเกิดสิวได้บ่อยคือช่วงวัยรุ่นจนถึงวัยกลางคน ซึ่งคิดเป็นร้อยละ 85 ของกลุ่มประชากรอายุระหว่าง 12 ถึง 25 ปีทั่วโลกที่เป็นสิว ลักษณะสิบบางออกเป็น สิวอุดตัน

ต้นหัวเปิด สีวอดต้นหัวปิด สีวักเสปประเภท ตุ่ม หัวหนอง หัวช้าง และซิสต์ กลไกการเกิดสิว ได้แก่ (1) ภาวะการหนาตัวมากกว่าปกติและการหลุดลอกที่น้อยกว่าปกติของเซลล์ผิวในต่อมไขมัน (2) ภาวะการผลิตไขมันที่ต่อมไขมันได้ผิวหนังที่มากกว่าปกติและองค์ประกอบของไขมันที่เปลี่ยนแปลงไป (3) ความไม่สมดุลของแบคทีเรียบนผิวหนัง และ 4. กระบวนการอักเสบของผิวหนัง

เนื่องจากโรคสิวเป็นการอักเสบเรื้อรังของผิวหนัง แม้มียารักษามากมายหลายแขนงแต่การตอบสนองต่อการรักษาของแต่ละบุคคลกลับแตกต่างกันออกไป ด้วยเหตุนี้จึงนำมาสู่การศึกษาวิจัยเพิ่มเติมเพื่อหาตัวยาใหม่ ๆ มาช่วยเสริมในการรักษาสิว

‘กรดทรานเอกซามิค’ หรือที่คนทั่วไปรู้จักกันในนาม ‘ทรานซามีน’ เป็นตัวยาที่ใช้ในการรักษาโรคฝ้า และพบว่ายังสามารถนำมาใช้ในการรักษาโรคสิวอักเสบร่วมได้เป็นอย่างดี จากการศึกษาวิจัยพบว่ากรดทรานเอกซามิคสามารถลดจำนวนสิวอักเสบได้อย่างมีประสิทธิภาพหลังการใช้ 4 สัปดาห์ และยังพบว่าอาสาสมัครส่วนหนึ่งมีรอยยุบในใบหน้าในบริเวณที่มีการทายากรดทรานเอกซามิคร่วมด้วย จึงทำให้เกิดข้อสันนิษฐานถึงคุณสมบัติในการลอกผิวชั้นหนังกำพร้า (ชั้นซีไคล) ร่วมด้วย

เมื่อกล่าวถึงคุณสมบัติในการลอกผิว จึงคิดว่ากรดทรานเอกซามิคอาจมีคุณสมบัติที่เทียบเคียงกับกรดผลไม้ที่มีฤทธิ์เป็นกรดอ่อนอย่างกรดอัลฟาไฮดรอกซี (Alpha Hydroxy acid) หรือกรดเอเอชเอ (AHA) และกรดเบต้าไฮดรอกซี (Beta Hydroxy acid) หรือกรดบีเอชเอ (BHA) หรือที่รู้จักกันในนามของกรดซาลิไซลิก (Salicylic acid) ที่พบในผลไม้รสเปรี้ยวเช่น มะนาว แอปเปิ้ล และนมเปรี้ยว ที่มักใช้เป็นส่วนผสมในผลิตภัณฑ์ความงามต่างๆ ในการผลัดเซลล์ผิวเก่าที่ตายไปแล้วและกระตุ้นให้มีการสร้างเซลล์ผิวใหม่ขึ้นมาทดแทน เป็นผลทำให้ผู้ใช้มีผิวที่เรียบเนียนขึ้น สิวผดผื่นลดลง ลดรอยหมองคล้ำ จุดดำจุดแดง และลดริ้วรอยบนใบหน้า ทำให้ดูอ่อนเยาว์ขึ้น

ดังนั้นการทํารวจในครั้งนี้มีวัตถุประสงค์เพื่อทดสอบประสิทธิภาพของการลอกผิวชั้นหนังกำพร้าบางส่วนของกรดทรานเอกซามิคในรูปแบบที่เป็นอิมัลเจลที่ความเข้มข้น 15% ทางเราคาดหวังว่าการศึกษานี้จะนำมาซึ่งประโยชน์ในด้านวิชาการทางการแพทย์ เพื่อเพิ่มประสิทธิภาพ และทางเลือกในการรักษาโรคสิพร่วมทั้งบำรุงฟื้นฟูผิวอีกต่อหนึ่ง

ท่านได้รับเชิญให้เข้าร่วมในโครงการวิจัยนี้เพราะคุณสมบัติที่เหมาะสมดังต่อไปนี้

1. เพศหญิง ชาวไทย อายุระหว่าง 18 – 25 ปี สุขภาพแข็งแรงดี
2. ได้รับการวินิจฉัยว่าเป็นโรคสิวอักเสบระดับความรุนแรงน้อยถึงปานกลางโดยแพทย์ผิวหนัง
3. อาสาสมัครยินยอมเข้าร่วมงานวิจัยด้วยความสมัครใจและลงลายลักษณ์อักษรในใบยินยอมเข้าร่วมโครงการ
4. ยินดีปฏิบัติตามข้อปฏิบัติและเงื่อนไขต่าง ๆ ตามที่ได้แจ้งจนจบการทดลอง

ท่านไม่สามารถเข้าร่วมในโครงการวิจัย หากท่านมีคุณสมบัติดังต่อไปนี้

1. มีประวัติแพ้กรดทราเอกซามิคจากการใช้มาก่อน
2. ประวัติเลือดออกในสมอง ลิ่มเลือดอุดตันในเส้นเลือดแดงหรือเส้นเลือดดำ หรือมีภาวะการเกิดลิ่มเลือดผิดปกติอยู่
3. ตั้งครรภ์หรือให้นมบุตรอยู่ หรือวางแผนมีบุตร
4. คุณก่ำนิดด้วยยาฮอร์โมนจากยาทาน ยาฉีด หรือยาฝังใต้ท้องแขน
5. โรคประจำตัวที่รุนแรงหรือที่ควบคุมไม่ได้ เช่นโรคเบาหวาน โรคความดันสูง โรคหัวใจ โรคทางระบบประสาทส่วนกลาง โรคไต โรคมะเร็ง หรือ โรคภูมิคุ้มกันบกพร่อง
6. ประวัติการใช้ยาหรือได้รับการรักษาสิวภายในระยะเวลา 1 เดือนก่อนเริ่มการวิจัย ตามข้อใดข้อหนึ่งดังต่อไปนี้
 - ✓ ได้รับยารับประทาน ได้แก่ กลุ่มวิตามินเอ ยาฮอร์โมน (เช่น ยาคูมก่ำนิด) ยาปฏิชีวนะ (เช่น เตตราไซคลิน ด็อกซีไซคลิน อิริโทรไมซิน และ อะม็อกซิซิลลิน)
 - ✓ ได้รับยาทาในกลุ่มยาฆ่าเชื้อ ลดการอักเสบ ลดการอุดตันของหัวสิว เช่น เบนโซอิลเพอร์ออกไซด์ วิตามินเอ และในกลุ่มของการลอกผิวชั้นหนังกำพร้า เช่น กรดเอเอชเอ และ กรดบีเอชเอ
 - ✓ อยู่ระหว่างการรักษาสิว เช่น เลเซอร์ กดสิว ลอกผิว เป็นต้น
7. โรคทางผิวหนัง เช่น โรคผื่นภูมิแพ้ผิวหนัง โรคผิวหนังอักเสบ หรือ โรคสะเก็ดเงิน
8. ความผิดปกติของฮอร์โมนเพศ เช่น ภาวะถุงน้ำรังไข่หลายใบ หรือ โรคเนื้องอกต่อมใต้สมองที่มีผลต่อการผลิตฮอร์โมน ที่มากเกินไป

ท่านอาจถูกคัดออกจากโครงการวิจัยขณะดำเนินโครงการอยู่ หากท่านมีคุณสมบัติดังต่อไปนี้

- พบผลตรวจว่าแพ้สารทราเอกซามิค 15% จากการทดสอบผื่นแพ้สัมผัส
- พบผลตรวจว่าแพ้ยาหลังจากการทดสอบผื่นแพ้สัมผัส
- อาสาสมัครมีความประสงค์ต้องการออกจากงานวิจัย
- อาสาสมัครไม่สามารถทนต่ออาการข้างเคียงที่มาจากการรักษาได้ หรือเกิดภาวะแทรกซ้อนรุนแรง
- อาสาสมัครไม่สามารถปฏิบัติตามข้อปฏิบัติและเงื่อนไขต่างๆตามที่ได้แจ้งไว้ เช่น ห้ามใช้ผลิตภัณฑ์ยารักษาสิวดูอื่นนอกเหนือจากที่แพทย์ผู้ทำวิจัยจัดไว้ให้ในระหว่างทำการทดลอง
- อาสาสมัครที่ไม่สามารถมาติดตามผลการรักษาได้

สถานที่ทำการวิจัย และจำนวนผู้เข้าร่วมในโครงการวิจัย

โรงพยาบาล มหาวิทยาลัยแม่ฟ้าหลวง กรุงเทพมหานคร

38/11-13 อาคารโศกเพลส สุขุมวิท 21 ถ.โศก เขตวัฒนา กรุงเทพมหานคร

โทรศัพท์ : 02-6642295

วิธีดำเนินการวิจัย

การวิจัยนี้เป็นงานวิจัยเชิงการทดลองทางคลินิก ชนิดมีการสุ่มเลือกและแบ่งครึ่งหน้า เพื่อทดสอบประสิทธิผลของการลอกผิวชั้นหนังกำพร้าร่วมกับการรักษาสิวอักเสบระดับความรุนแรงน้อยถึงปานกลางด้วยกรดทราโนเอกซามิกในรูปแบบอิมัลเจิลที่ความเข้มข้น 15%

การดำเนินงานวิจัยมีขั้นตอนดังนี้

1. ท่านจะได้รับการซักประวัติทั่วไป ข้อมูลส่วนบุคคลของท่านจะมีการบันทึกเป็นเลขรหัสแทนตัวท่าน โดยจะไม่สามารถบ่งชี้ถึงตัวบุคคลของท่านได้
2. ทำการวินิจฉัยและประเมินระดับความรุนแรงของโรคสิวจากแพทย์ผิวหนัง
3. ชี้แจงรายละเอียดข้อมูลและขั้นตอนการปฏิบัติการวิจัย ผลข้างเคียงที่อาจจะได้รับ และข้อปฏิบัติหากมีอาการแพ้เฉียบพลัน กรอประวัติส่วนตัวในแบบสอบถาม และลงลายลักษณ์อักษรยินยอมเข้าร่วมโครงการวิจัย
4. ทำการทดสอบผื่นแพ้สัมผัสกับตัวยาที่ใช้ในการทำวิจัย ที่บริเวณท้องแขนช่วงบน เป็นระยะเวลา 2 วัน (48 ชั่วโมง) และทำการประเมินผล
5. ล้างหน้าให้สะอาดทุกครั้งก่อนทำการประเมินใบหน้าด้วยผลิตภัณฑ์ล้างหน้า Acne-Aid® Gentle cleanser
6. ทำการถ่ายภาพและวัดสภาพผิวหนังบริเวณใบหน้าด้วยเครื่องถ่ายภาพและเครื่องมือต่างๆ ประเมินตำแหน่งและความรุนแรงของโรคสิว ตรวจวัดระดับการระเหยของน้ำออกจากผิวและวัดระดับความมันของผิว
7. ท่านอาจจะได้รับการสุ่มเลือกจากผู้วิจัย เพื่อทำการลอกผิวชั้นหนังกำพร้า (ชั้นซีไค) ด้วยเทปใสที่บริเวณใต้คางสองข้าง โดยมีจำนวนอาสาสมัครที่มีโอกาสได้รับการสุ่มเลือก 4 คน จากอาสาสมัครทั้งหมดในโครงการ 19 คน
8. ท่านจะได้รับยาอิมัลเจิลทาบนบริเวณใบหน้าและใต้คางจำนวน 2 หลอดที่มีลักษณะเหมือนกัน ทายาตามฉลากกำกับ โดยให้เริ่มจากหลอดยาหมายเลข 1 ทาครึ่งหน้าก่อนแล้วค่อยตามด้วยหลอดยาหมายเลข 2 ทาอีกครึ่งหน้า

วิธีการใช้

1) ล้างมือและล้างหน้าให้สะอาดก่อนทายาทุกครั้ง ผู้วิจัยสนับสนุนผลิตภัณฑ์ล้างหน้า Acne-Aid® Gentle cleanser แทนสบู่ล้างหน้าที่ใช้เป็นประจำ

2) บีบอิมัลเจลจากหลอดยาหมายเลข 1 เป็นเส้นตรงยาวเท่ากับ 1 ข้อนิ้วของนิ้วชี้ บีบ 2 ครั้ง แล้วแต้มไปบนบริเวณหน้าผาก แก้ม จมูก คาง และใต้คาง ที่บริเวณครึ่งผึ่งของใบหน้าตามคำอธิบายในฉลาก แล้วเกลี่ยเนื้ออิมัลเจลให้ครอบคลุมทั่วทั้งใบหน้าและใต้คาง แล้วต่อด้วยการทายาจากหลอดยาหมายเลข 2 ครึ่งหน้าตามคำอธิบายในฉลาก

3) ใช้มือขวาทาเจลบนใบหน้าซีกขวา และมือซ้ายทาเจลบนใบหน้าซีกซ้าย

4) ทาอิมัลเจลทุกวัน ๆ ละ 2 เวลา เช้า - เย็น เป็นเวลา 2 เดือนติดต่อกัน

9. นัดติดตามอาการอาสาสมัครทุกอาทิตย์เป็นเวลา 4 อาทิตย์ และอาทิตย์ที่ 8 ซึ่งเป็นที่สุดท้าย

10. ท่านสามารถใช้ครีมป้องกันแดดและผลิตภัณฑ์ความงามได้ตามปกติในระหว่างการศึกษาวิจัยครั้งนี้ นอกจากการใช้ครีมกันแดดแล้ว ท่านยังสามารถลดการสัมผัสกับแสงแดดโดยตรงได้ด้วยแว่นตากันแดด หน้ากากอาานามัย หมวกป้องกันแดด และร่มป้องกันแดดได้

**** หมายเหตุ** เนื่องจากยาทามีฤทธิ์เป็นกรดอ่อน หลังทาครีมบนใบหน้า หน้าจะมีอาการแห้งแดงระเรื่อ และมีการลอกตัวเป็นขุยเล็กน้อย ซึ่งเป็นไปตามเป้าหมายของการทำวิจัย แต่หากท่านไม่สามารถทนอาการข้างเคียงได้ หรือมีอาการอื่นที่ไม่พึงประสงค์เกิดขึ้น ให้หยุดการใช้ยาและรีบติดต่อมายังแพทย์ผู้ทำวิจัยทันทีเพื่อทำการประเมินสภาพหน้าและทำการแก้ไขรักษาต่อไป อาสาสมัครมีสิทธิ์ถอนตัวออกจากโครงการวิจัยได้ก่อนกำหนดโดยไม่มีผลต่อการรักษาอันพึงได้รับ

ความรับผิดชอบของผู้เข้าร่วมในโครงการวิจัย

1. ทาอิมัลเจลตามวิธีการใช้อย่างเคร่งครัด เป็นประจำทุกวัน วันละ 2 ครั้ง และไม่ทาสลับข้างกัน

2. จดใช้ยาหรือรักษาสิวด้วยวิธีอื่นนอกเหนือจากที่ผู้วิจัยจัดให้ และหากท่านได้รับยาอื่น ๆ ขอให้แจ้งให้ผู้วิจัยทราบ

3. สังเกตอาการผลข้างเคียงและแจ้งอาการผิดปกติที่เกิดขึ้นโดยเร็วให้ผู้วิจัยทราบ

4. ให้ความร่วมมือในทุกด้านและปฏิบัติตามคำชี้แนะจากทีมงานวิจัยในขณะทำการทดลอง

5. มารับการรักษาตามนัดทุกครั้ง

ความไม่สบาย หรือความเสี่ยงที่อาจเกิดขึ้น และการดูแลรักษา

ผลข้างเคียงที่มีรายงานว่าสามารถพบได้ คือ อาการผิวด่าง แห้ง ลอกมีขุย แสบหรือมีอาการคันซึ่งเป็นอาการที่พบได้หลังทากรดทรานเอกซามิก โดยทั่วไปมักมีอาการน้อยและอาการมักจะหายได้เอง แนะนำให้หลีกเลี่ยงการล้างหน้าด้วยน้ำอุ่น โดนแสงแดดและการแกะเกา

กรณีการรักษาด้วย Tranexamic acid ได้ผล หลังการศึกษาผู้วิจัยจะสนับสนุนครีมที่มีตัวยา Tranexamic acid ให้แก่อาสาสมัครเพื่อรักษารอยสิวและปรับสภาพผิวทั้งสองข้างให้เท่ากัน

กรณีที่ท่านมีอาการมากหรือมีความกังวล แนะนำให้ท่านแจ้งแพทย์ผู้ทำการวิจัยทันทีและอาจมาพบแพทย์นอกตารางนัดหมายเพื่อประเมินอาการ อาจมีการพิจารณาให้หยุดทำการทดลองและทำการรักษาด้วยวิธีต่าง ๆ ตามมาตรฐานการรักษาต่อไป

หากมีอันตรายที่เกิดขึ้นจากการวิจัย และท่านปฏิบัติตามคำแนะนำของทีมงานวิจัย ท่านจะได้รับการรักษาอย่างเหมาะสม ผู้วิจัยจะรับผิดชอบค่าใช้จ่ายในการรักษาพยาบาล รวมทั้งการชดเชยการสูญเสียเวลาและรายได้ตามความเหมาะสม

ประโยชน์ที่คาดว่าจะได้รับจากโครงการวิจัย

1. ทำให้อาสาสมัครมีสภาพผิวที่ดีขึ้น ระดับความรุนแรงและจำนวนของสิวลดลง
2. ผลการวิจัยที่ได้จะเป็นความรู้ทางการแพทย์เพื่อเพิ่มประสิทธิภาพและเพิ่มทางเลือกในการรักษาโรคผิวหนังอักเสบโดยใช้กรดทรานเอกซามิก
3. เพื่อใช้เป็นข้อมูลพื้นฐานในการทำวิจัยต่อไปในอนาคต
4. การเข้าร่วมในโครงการวิจัยนี้อาจจะทำให้ท่านมีสภาพผิวที่ดีขึ้น หรืออาจจะลดความรุนแรงของโรคสิวลดลง แต่ไม่สามารถรับรองได้ว่า สภาพผิวของท่านจะต้องดีขึ้นหรือความรุนแรงของโรคสิวลดลงอย่างแน่นอน

ทางเลือกอื่น หากไม่เข้าร่วมในโครงการวิจัย

ท่านไม่จำเป็นต้องเข้าร่วมในโครงการวิจัยนี้ เนื่องจากมีแนวทางการรักษาด้วยวิธีอื่น หรือโรงพยาบาลอื่น สำหรับการรักษาอาการผิวหนังอักเสบและการดูแลเรื่องการผลัดผิวของท่านได้ ดังนั้น ท่านควรปรึกษากับแพทย์ของท่าน ก่อนตัดสินใจเข้าร่วมในโครงการวิจัย

ค่าใช้จ่ายที่ผู้เข้าร่วมในโครงการวิจัยจะต้องรับผิดชอบ

ไม่มีค่าใช้จ่ายใด ๆ ในการเข้าร่วมโครงการวิจัยครั้งนี้

ค่าตอบแทนที่จะได้รับ เมื่อเข้าร่วมในโครงการวิจัย

ท่านจะได้รับเงินค่าเดินทางและค่าเสียเวลาในการมาพบแพทย์ครั้งละ 200 บาท จำนวน 7 ครั้ง รวมเป็นเงิน 1,400 บาท

การรักษาความลับของข้อมูล

ข้อมูลทั้งหมดที่เกี่ยวข้องกับงานวิจัยจะถูกเก็บไว้เป็นความลับ มีเพียงคณะผู้ทำวิจัยเท่านั้นที่สามารถเข้าถึงข้อมูลได้ ข้อมูลส่วนบุคคลที่ระบุตัวตนของท่านจะไม่ถูกบันทึกในเอกสารงานวิจัยแต่จะบันทึกเป็นเลขรหัสแทน คณะผู้ทำวิจัยจะทราบแค่เพียงเลขรหัสที่กำหนดมาเพื่อเป็นตัวแทนของท่านเท่านั้น ผลของงานวิจัยใช้สำหรับวัตถุประสงค์ทางวิชาการเท่านั้น โดยจะเผยแพร่เฉพาะผลสรุปงานวิจัย โดยที่จะไม่มีการระบุถึงข้อมูลส่วนบุคคลของอาสาสมัคร จะไม่เปิดเผยชื่อนามสกุล ที่อยู่ ของท่านเป็นรายบุคคล โดยข้อมูลส่วนบุคคลต่าง ๆ จะถูกเก็บไว้และไม่มีการเผยแพร่สู่สาธารณชน

สำหรับข้อมูลภาพถ่ายดิจิทัลของอาสาสมัครจะใช้เพื่องานวิจัยนี้เท่านั้น มีการคาดสืดำทับบริเวณตาทั้งสองข้างเพื่อปกปิดตัวตนของอาสาสมัคร จะไม่ระบุตัวตนของท่านและจะไม่ถูกนำไปใช้ในงานวิจัยอื่น ๆ ภายหลังเสร็จสิ้นโครงการวิจัย ข้อมูลที่เป็นรูปภาพของอาสาสมัครจะถูกลบทิ้ง ไม่มีการเก็บไว้

การถอนตัวหรือการสิ้นสุดการเข้าร่วมในโครงการวิจัย

หากท่านไม่สมัครใจจะเข้าร่วมการศึกษาแล้ว ท่านสามารถถอนตัวได้ตลอดเวลา การขอถอนตัวออกจากโครงการวิจัยจะไม่มีผลต่อการดูแลรักษาโรคหรือสิทธิต่าง ๆ ที่ท่านพึงได้รับ

การติดต่อหากมีคำถามเกี่ยวกับการวิจัย

หากมีคำถามเกี่ยวข้องกับการวิจัย หรือเกิดอันตรายใด ๆ ท่านสามารถติดต่อแพทย์หญิงชลธิ์ เชื้อชวลิต เบอร์โทรศัพท์ 0611956493 หรือ 0922652416 ได้ตลอด 24 ชั่วโมง หรือติดต่ออาจารย์ที่ปรึกษา แพทย์หญิงสิรินทิพย์ ชัยชลทรกุล เบอร์โทรศัพท์ 086-5172017

หากท่านได้รับการปฏิบัติที่ไม่เป็นธรรมในโครงการวิจัยนี้ ท่านสามารถติดต่อได้ที่ ห้องปฏิบัติการคณะกรรมการจริยธรรมการวิจัยในมนุษย์ มหาวิทยาลัยแม่ฟ้าหลวง อาคารบริการวิชาการ (AS) ชั้น 4 มหาวิทยาลัยแม่ฟ้าหลวง โทรศัพท์ 053-917-170 ถึง 71 โทรสาร 053-917-170 หรืออีเมล rec.human@mfu.ac.th

หากมีข้อมูลใหม่เกี่ยวข้องกับการวิจัย

ผู้วิจัยจะต้องแจ้งให้ท่านทราบหากมีข้อมูลใหม่ที่เกี่ยวข้องกับการวิจัยเพื่อให้ท่านตัดสินใจว่า จะยังคงเข้าร่วมหรือถอนตัวจากโครงการวิจัยนี้

ข้อพิจารณาด้านจริยธรรม

1. อาสาสมัครทุกท่านจะได้รับข้อมูลเกี่ยวกับงานวิจัย ตั้งแต่วัตถุประสงค์ รวมถึงขั้นตอนต่าง ๆ ในการวิจัย อาการและผลข้างเคียงอันไม่พึงประสงค์ซึ่งอาจเกิดขึ้นได้ โดยแพทย์ผู้ทำวิจัยจะอธิบายอย่างละเอียด และผู้เข้าร่วมวิจัยลงชื่อยินยอมเข้าร่วมโครงการเป็นลายลักษณ์อักษรด้วยความสมัครใจ
2. ในการทำวิจัยครั้งนี้ผู้เข้าร่วมวิจัยจะไม่มีการเสียค่าใช้จ่ายใด ๆ
3. กรณีเกิดผลข้างเคียง อาการไม่พึงประสงค์ ผู้วิจัยจะรับผิดชอบดูแลอาสาสมัครตั้งแต่เกิดอาการไม่พึงประสงค์จนอาสาสมัครหายเป็นปกติและรับผิดชอบค่าใช้จ่ายในการรักษาพยาบาลทั้งหมด
4. กรณีเกิดผลข้างเคียงอาสาสมัครมีสิทธิในการถอนตัวออกจากโครงการวิจัยได้ทุกเมื่อ
5. ข้อมูลส่วนตัวของผู้เข้าร่วมวิจัยทั้งหมดจะถูกเก็บไว้เป็นความลับ แต่ข้อมูลเกี่ยวกับผลการรักษาอาจถูกเปิดเผยต่อสาธารณะเพื่อประโยชน์ทางวิชาการโดยไม่มีการระบุชื่อของผู้เข้าร่วมวิจัย
6. งานวิจัยได้ผ่านการพิจารณาทางด้านจริยธรรมโดยคณะกรรมการของมหาวิทยาลัยแม่ฟ้าหลวงแล้ว

หากท่านตกลงเข้าร่วมการศึกษาวิจัยในครั้งนี้ ท่านจะมีข้อปฏิบัติร่วมดังต่อไปนี้

1. อาสาสมัครจะได้รับการรักษาตามที่กำหนดไว้และมีการตรวจติดตาม ท่านต้องมาตามแพทย์นัดทุกครั้ง
2. หลังการรักษาแพทย์ผู้ทำการวิจัยจะให้อาสาสมัครกรอกใบประเมินผลการรักษา กรณกรอกใบประเมินตามความเป็นจริงเพื่อแพทย์ผู้ทำการวิจัยจะได้นำไปใช้ในการวิเคราะห์ข้อมูลต่อไป
3. การเข้าร่วมโครงการนี้เป็นไปด้วยความสมัครใจ อาสาสมัครสามารถถอนตัวจากโครงการวิจัยได้ทุกเมื่อโดยไม่กระทบกับการรักษาที่พึงได้รับ
4. ผลการศึกษาที่ใช้สำหรับวัตถุประสงค์ทางวิชาการเท่านั้น โดยข้อมูลส่วนบุคคลต่าง ๆ จะถูกเก็บไว้และไม่มีการเผยแพร่สู่สาธารณชน ขอรับรองว่าจะไม่มีการเปิดเผยชื่อของท่านตามกฎหมาย

ขอขอบพระคุณในความร่วมมือของท่านมา ณ ที่นี้

แพทย์หญิงชวลี เชื้อขวลิต

APPENDIX C

INFORMED CONSENT

หนังสือแสดงเจตนายินยอมเข้าร่วมในโครงการวิจัย สำหรับอาสาสมัคร

(Informed Consent)

ชื่อโครงการวิจัย การศึกษาผลของการลอกผิวจากกรดทรานเอกซามิค 15% ในการรักษาสิวอักเสบ

ข้าพเจ้านาง/นางสาว.....

ที่อยู่.....

ได้อ่านรายละเอียดจากเอกสารชี้แจงข้อมูลแก่อาสาสมัครผู้เข้าร่วมในโครงการวิจัย ฉบับวันที่

ข้าพเจ้าได้รับสำเนาเอกสารชี้แจงข้อมูลแก่อาสาสมัครผู้เข้าร่วมในโครงการวิจัยและสำเนาเอกสารแสดง

เจตนายินยอมเข้าร่วมในโครงการวิจัยที่ข้าพเจ้าได้ลงนามและลงวันที่ ทั้งนี้ก่อนที่จะลงนามข้าพเจ้าได้รับการ อธิบายโดยละเอียดจากผู้วิจัยถึงวัตถุประสงค์ วิธีการวิจัย ความไม่สุขสบายหรือความเสี่ยงที่อาจเกิดขึ้นประโยชน์ ที่คาดว่าจะได้จากการวิจัย และทางเลือกอื่น

ข้าพเจ้ามีเวลาและโอกาสเพียงพอในการซักถามข้อสงสัย โดยผู้วิจัยได้ตอบคำถามต่าง ๆ ด้วยความเต็มใจ ไม่ปิดบังซ่อนเร้นจนข้าพเจ้าเข้าใจเป็นอย่างดีแล้ว

ข้าพเจ้ารับทราบจากผู้วิจัยว่า หากเกิดอันตรายใด ๆ จากการวิจัย ข้าพเจ้าจะได้รับการรักษาพยาบาลตาม ที่ระบุในเอกสารชี้แจงข้อมูลแก่อาสาสมัครผู้เข้าร่วมในโครงการวิจัย

ข้าพเจ้ามีสิทธิที่จะถอนตัวออกจากโครงการวิจัยเมื่อใดก็ได้ การถอนตัวนี้ไม่มีผลต่อการรักษาพยาบาล และสิทธิอื่นๆที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับ การรายงานสรุปผลการวิจัยจะไม่ระบุ ชื่อนามสกุลของข้าพเจ้า การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงาน ต่างๆที่เกี่ยวข้องจะกระทำด้วยเหตุ ผลทางวิชาการเท่านั้น

ข้าพเจ้าได้อ่านข้อความข้างต้นและมีความเข้าใจดีทุกประการแล้ว ยินดีเข้าร่วมในการวิจัยด้วยความ สมัครใจ จึงได้ลงนามในเอกสารและแสดงความยินยอมนี้

..... ลงนามผู้เข้าร่วมในโครงการ
 (.....)
 วันที่.....เดือน.....พ.ศ.....

ข้าพเจ้าได้อธิบายโดยละเอียดถึงวัตถุประสงค์ วิธีการวิจัยความไม่สุขสบายหรือความเสี่ยงที่
 อาจเกิดขึ้น ประโยชน์ที่คาดว่าจะได้รับจากการวิจัยและทางเลือกอื่นให้ผู้เข้าร่วมในโครงการวิจัยได้
 ทราบและมีความเข้าใจดี แล้ว พร้อมทั้งลงนามในเอกสารแสดง เจตนายินยอมด้วยความสมัครใจ

..... ลงนามผู้วิจัย
 (.....แพทย์หญิง ขวดี เชื้อขวลิต.....)

..... ลงนามพยาน
 (.....)

..... ลงนามพยาน
 (.....)
 วันที่.....เดือน.....พ.ศ.....

APPENDIX D

PATIENT RECORD FORM

(Medical History)

เลขรหัส

วันที่เก็บข้อมูล.....

เรื่อง: โครงการวิจัย การศึกษาผลการผลัดเซลล์ผิวชั้นหนังกำพร้าจากกรดทราเนอซามิก 15% ใน
การรักษาสิวอักเสบ

The Peeling Effect of Topical 15% Tranexamic acid in Inflammatory Acne

ข้อมูลทั่วไป

1. รหัส อายุ ปี
2. สัญชาติ
3. เพศ หญิง.....
4. ที่อยู่

☐ กรุงเทพฯ
 ☐ ต่างจังหวัด
 ☐ ต่างประเทศ
5. อาชีพ

☐ รับราชการ
 ☐ แม่บ้าน
 ☐ พนักงานทั่วไป

☐ กิจการส่วนตัว
 ☐ นักเรียนนักศึกษา
 ☐ อื่นๆ ระบุ

โรคประจำตัว

- ☐ ไม่มี
- ☐ มี

โปรด ระบุ

ยารักษาโรค อาหารเสริม วิตามิน ที่ทานเป็นประจำ

- ☐ ไม่มี
- ☐ มี

โปรด ระบุ

ประวัติแพ้ยา

- ☐ ไม่มี
- ☐ มี โปรด ระบุ.....

ข้อมูลทางนาฬิกา

1. วันแรกของการมีประจำเดือนครั้งสุดท้ายคือวันที่
☐ หหมดประจำเดือนแล้ว
2. ประวัติการคุมกำเนิด
☐ ไม่ได้คุมกำเนิด ☐ คุมกำเนิด โดยวิธี โปรดระบุ
3. ท่านกำลังตั้งครรภ์อยู่หรือไม่
☐ ใช่ ☐ ไม่ใช่
4. ท่านกำลังให้นมบุตรอยู่หรือไม่
☐ ใช่ ☐ ไม่ใช่
5. ท่านกำลังวางแผนมีบุตรหรือไม่
☐ ใช่ ☐ ไม่ใช่

ประวัติเกี่ยวกับสิว

1. ท่านเป็นสิวที่ใบหน้ามานานเท่าไร
 เริ่มเป็นสิวครั้งแรกเมื่ออายุ ปี
2. เคยมีเวลาเว้นช่วงที่หายจากการเป็นสิว หรือไม่
☐ มี ☐ ไม่มี เป็นสิวเรื้อรังอยู่ตลอดเวลา
3. ท่านคิดว่าอะไรเป็นปัจจัยกระตุ้นให้ท่านเกิดสิว
☐ ผิวมัน ☐ ประจำเดือน ☐ เครื่องสำอาง
☐ อาหาร โปรดระบุ
☐ อื่น ๆ โปรดระบุ

ประวัติการรักษาสิว

1. ในช่วง 1 เดือนที่ผ่านมา ท่านได้ใช้ยาทาหรือยากินรักษาสิวหรือไม่
☐ ไม่ใช่ ☐ ใช่ โปรดระบุ
2. ในช่วง 1 เดือนที่ผ่านมา ท่านได้รักษาสิวด้วยเลเซอร์หรือแสงรักษาสิวชนิดอื่นหรือไม่
☐ ไม่ใช่ ☐ ใช่ โปรดระบุ
3. ในช่วง 1 เดือนที่ผ่านมา ท่านได้รักษาสิวด้วยวิธีอื่นหรือไม่
☐ ไม่ใช่ ☐ ใช่ โปรดระบุ

APPENDIX E

DOCTOR RECORD FORM

สัปดาห์ที่

เลขรหัส

วันที่เก็บข้อมูล.....

1. VISIA® Skin Analysis System

☐ ใบหน้าตรง ☐ ใบหน้าด้านขวา ☐ ใบหน้าด้านซ้าย

2. Desquamation

a. Visioscan® VC 98

☐ Real image ☐ Corneoflix

b. Physical examination

SCALING		
SCORE	GRADE	DESCRIPTION
0	None	No scaling
1	Mild	Barely perceptible, fine scales present to limited areas of the face
2	Moderate	Fine scale generalized to all areas of the face
3	Severe	Scaling and peeling of skin over all areas of the face

Scaling score

ใบหน้าข้างขวา

ใบหน้าข้างซ้าย

คะแนน = ...

คะแนน = ...

เกรด = ...

เกรด = ...

3. Wrinkle

a. VISIA® Skin Analysis

Right periorbital fine lines

Left periorbital fine lines

b. Physical Examination

6. Acne

a. Acne lesion count

ใบหน้าข้าง ขวา							ใบหน้าข้าง ซ้าย						
	หน้าผาก	แก้ม	จมูก	คาง	ใต้คาง	ผลรวม		หน้าผาก	แก้ม	จมูก	คาง	ใต้คาง	ผลรวม
สิวอุดตัน							สิวอุดตัน						
ชนิดปิด (close)							ชนิดปิด (close)						
ชนิดเปิด (open)							ชนิดเปิด (open)						
ผลรวม							ผลรวม						
สิวอักเสบ							สิวอักเสบ						
สิวดม (papule)							สิวดม (papule)						
สิิวหัวหนอง (pustule)							สิิวหัวหนอง (pustule)						
สิิวหัวช้าง (nodule)							สิิวหัวช้าง (nodule)						
สิิวหัวซิสต์ (cyst)							สิิวหัวซิสต์ (cyst)						
ผลรวม							ผลรวม						

ใบหน้าข้างขวา

ใบหน้าข้างซ้าย

จำนวนสิวย่น = ...

จำนวนสิวย่น = ...

จำนวนสิวย่นอักเสบ = ...

จำนวนสิวย่นอักเสบ = ...

b. Evaluator's Acne Severity Grading

TABLE 1. Evaluator's global acne severity scale		
GRADE	VALUE	DEFINITION
Clear	0	Normal, clear skin with no evidence of acne vulgaris
Almost clear	1	Rare noninflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
Mild	2	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulocystic lesions)
Moderate	3	Noninflammatory lesions predominate, with multiple inflammatory lesions evident; several to many comedones and papules/pustules; there may or may not be one small nodulocystic lesion
Severe	4	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
Very severe	5	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules, and many nodulocystic lesions

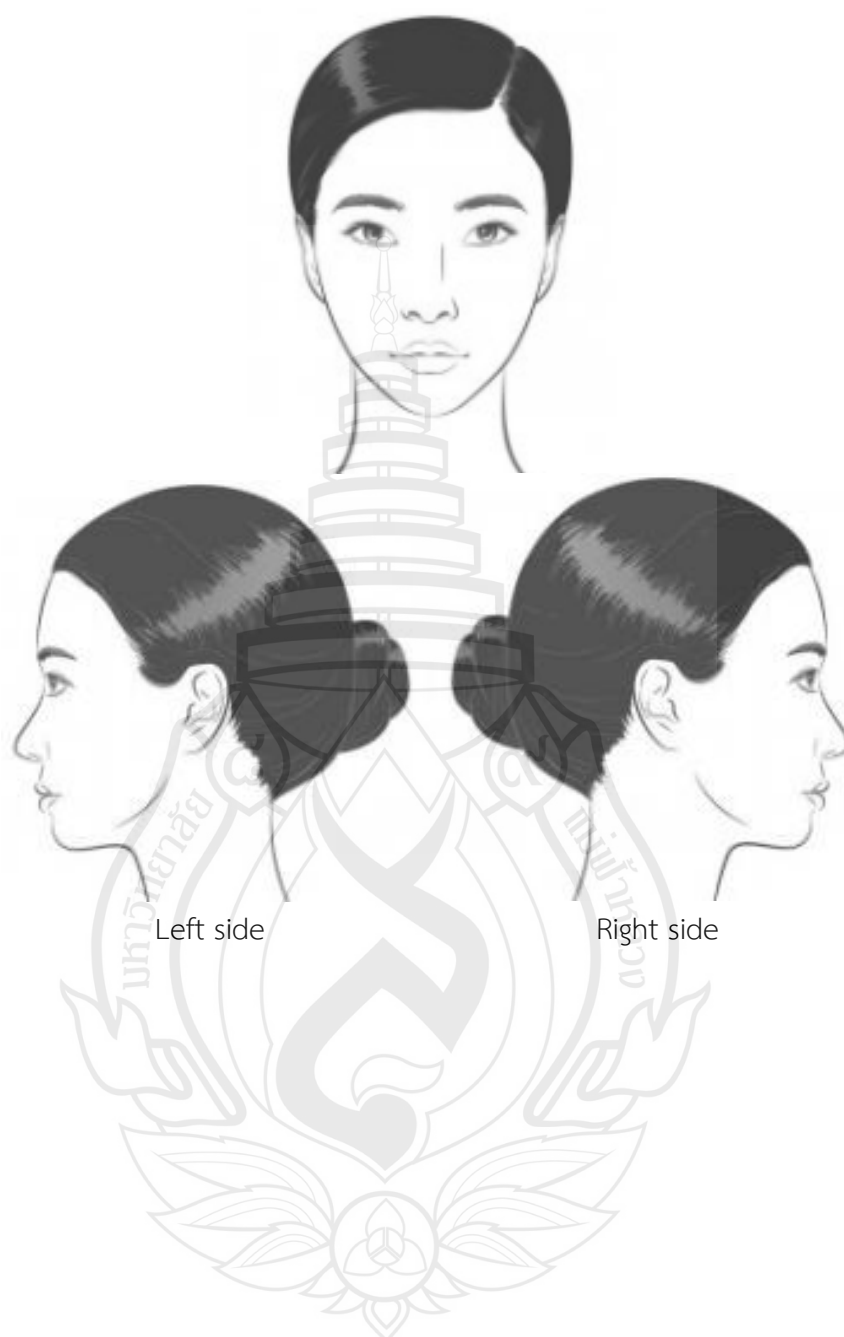
From: Schlessinger J, Menter A, Gold M, et al. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol*. 2007;6: 607-615.¹¹

Acne grading

ใบหน้าข้างขวา:

ใบหน้าข้างซ้าย:

c. Acne Location



APPENDIX F

PATIENT RECORD FORM

Satisfaction Form

สัปดาห์ที่

เลขรหัส

วันที่เก็บข้อมูล.....

1.1 Global Patient Satisfaction Scale (ประเมินโดยอาสาสมัคร)

ความพึงพอใจ		ในหนังสือด้านขวา		ในหนังสือด้านซ้าย
การลดลงของจำนวนชีวิตและระดับ ความรุนแรงของชีวิต	1	ไม่พอใจมาก	1	ไม่พอใจมาก
	2	ไม่พอใจ	2	ไม่พอใจ
	3	ปานกลาง	3	ปานกลาง
	4	พอใจ	4	พอใจ
	5	พอใจมาก	5	พอใจมาก
การลดลงของการอักเสบของชีวิต	1	ไม่พอใจมาก	1	ไม่พอใจมาก
	2	ไม่พอใจ	2	ไม่พอใจ
	3	ปานกลาง	3	ปานกลาง
	4	พอใจ	4	พอใจ
	5	พอใจมาก	5	พอใจมาก
การเกิดขุย	1	ไม่พอใจมาก	1	ไม่พอใจมาก
	2	ไม่พอใจ	2	ไม่พอใจ
	3	ปานกลาง	3	ปานกลาง
	4	พอใจ	4	พอใจ
	5	พอใจมาก	5	พอใจมาก
การลดลงของรีวรอบคองตา	1	ไม่พอใจมาก	1	ไม่พอใจมาก
	2	ไม่พอใจ	2	ไม่พอใจ
	3	ปานกลาง	3	ปานกลาง
	4	พอใจ	4	พอใจ
	5	พอใจมาก	5	พอใจมาก

1.2 Product Satisfaction ขวา กับ ซ้าย (ประเมินโดยอาสาสมัคร)

ความพึงพอใจในด้าน	ระดับความพึงพอใจ				
	มากที่สุด	มาก	ปานกลาง	น้อย	น้อยที่สุด
สี					
กลิ่น					
เนื้อผลิตภัณฑ์					
ความหนืด					
การดูดซึม					

โปรดแสดงความคิดเห็นหลังการใช้ผลิตภัณฑ์หลอดเจลที่ (1) กับ (2) ว่ามีความแตกต่างกันอย่างไร และชอบหลอดเจลตัวไหนมากกว่ากัน

- หลอดเจลที่ 1 (ข้าง _____)

.....

.....

.....

.....

.....

- หลอดเจลที่ 2 (ข้าง _____)

.....

.....

.....

.....

.....

Side Effect Evaluation Form

ครั้งที่ สัปดาห์ที่

เลขรหัส

วันที่เก็บข้อมูล.....

1. Adverse effects (ประเมินโดยอาสาสมัคร)

ข้างขวา ข้างซ้าย

อาการข้างเคียงจากการหายาเฉพาะที่		
1. การลอกเป็นขุย (Scale)		
คะแนน	เกรต	ลักษณะ
0	ไม่มี	ผิวปกติ
1	รุนแรงน้อย	แทบมองไม่เห็นขุย หรือมีเล็กน้อยเฉพาะบางจุด
2	รุนแรงปานกลาง	มีขุยขนาดเล็ก กระจายทั่วทั้งใบหน้า
3	รุนแรงมาก	มีขุยหรือเกิดการลอกของผิวหนังอย่างเห็นได้ชัด กระจายทั่วทั้งใบหน้า
2. หน้าแดง (Erythema)		
คะแนน	เกรต	ลักษณะ
0	ไม่มี	สีผิวปกติ
1	รุนแรงน้อย	สีผิวออกชมพู
2	รุนแรงปานกลาง	สีผิวออกแดง
3	รุนแรงมาก	หน้าแดงอย่างชัดเจน สีผิวแดงสดถึงแดงคล้ำ
3. คัน (Itching)		
คะแนน	เกรต	ลักษณะ
0	ไม่มี	ไม่คัน
1	รุนแรงน้อย	คันเล็กน้อย ไม่ทำให้เกิดการข่วน
2	รุนแรงปานกลาง	คัน ทำให้เกิดการข่วน
3	รุนแรงมาก	คันมาก รบกวนการใช้ชีวิตประจำวัน และ/หรือ รบกวนการนอน
4. ปวดแสบร้อน (Burning)		
คะแนน	เกรต	ลักษณะ
0	ไม่มี	อาการปกติ
1	รุนแรงน้อย	อาการปวดแสบเล็กน้อย ไม่ทำให้เกิดการข่วน
2	รุนแรงปานกลาง	อาการปวดแสบ ร้อน ค่อนข้างรู้สึกข่วน
3	รุนแรงมาก	อาการปวดแสบร้อนมาก ทำให้รู้สึกไม่สบายกาย รบกวนการใช้ชีวิตประจำวัน และ/หรือ รบกวนการนอน
5. แสบ (Stinging)		
คะแนน	เกรต	ลักษณะ
0	ไม่มี	อาการปกติ
1	รุนแรงน้อย	อาการแสบเล็กน้อย ไม่ทำให้เกิดการข่วน
2	รุนแรงปานกลาง	อาการแสบ ค่อนข้างรู้สึกข่วน
3	รุนแรงมาก	อาการแสบมาก ทำให้รู้สึกไม่สบายกาย รบกวนการใช้ชีวิตประจำวัน และ/หรือ รบกวนการนอน

โปรดแสดงความคิดเห็นหลังการใช้ผลิตภัณฑ์หลอดเจลที่ (1) กับ (2) ว่ามีความแตกต่างกันอย่างไร และชอบหลอดเจลตัวไหนมากกว่ากัน

- หลอดเจลที่ 1 (ข้าง ____)

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.....

- หลอดเจลที่ 2 (ข้าง ____)

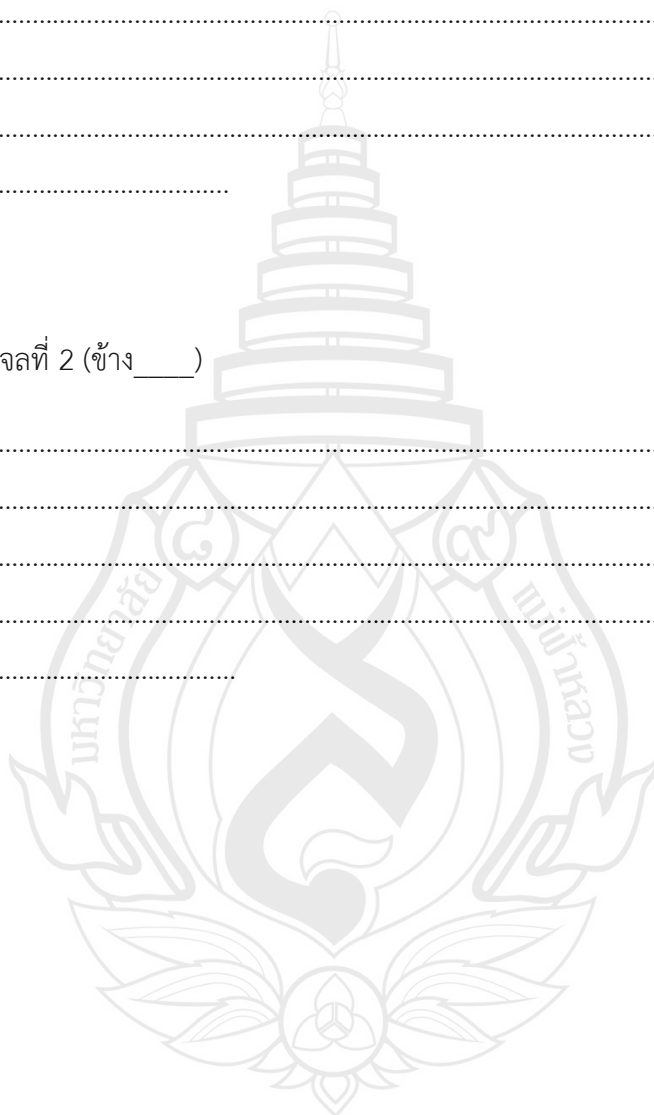
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APPENDIX G

PACKAGING AND LABELING



Both the 15% Tranexamic acid and the placebo gel were packaged in plastic tubes.

Other information sheets were included in the package



การประเมินระดับความรุนแรงของการลอกตัวของผิวหนังกำพืด

ลักษณะการลอกตัวของผิว				
ระดับการลอกตัวของผิว	ระดับ 0 (ผิวธรรมดา) ไม่มีการลอกตัวของผิว	ระดับ 1 (มีขุยเล็กน้อย) มองเห็นการลอกตัวของผิว หรืออาจสังเกตเห็นเป็นขุยเล็กๆบางจุดบนใบหน้า	ระดับ 2 (มีขุยปานกลาง) เห็นการลอกตัวของผิวที่ชัดเจนขึ้น ลักษณะเป็นขุยเล็กๆกระจายทั่วทั้งใบหน้า	ระดับ 3 (มีขุยมาก) มีการลอกตัวของผิวที่ชัดเจน ลักษณะเป็นขุยขนาดใหญ่หรือมีการลอกตัวของผิวเป็นแผ่นทั่วทั้งใบหน้า

ระดับการลอกตัวของผิวหนังกำพืด

ระดับ 0 – 1: ยอมรับได้

ระดับ 2: ยอมรับได้ ให้ทำการสังเกตการลอกของผิวอย่างใกล้ชิด สามารถปรึกษาแพทย์ผู้ทำวิจัยได้

ระดับ 3: หยุดการเข้ายา ติดต่อแพทย์ผู้ทำวิจัยทันที

อาการแพ้รุนแรงเฉียบพลัน (Anaphylaxis)

- ผื่นลมพิษ คัน ปากบวม ลิ้นบวม บริเวณรอบตาบวม
- หายใจติดขัด หายใจลำบาก หอบเหนื่อย หายใจมีเสียงหวีด
- แน่นหน้าอก เจ็บหน้าอก เป็นลม ความดันโลหิตซิสโตลลดลงต่ำกว่า 90 มิลลิเมตรปรอท
- ปวดท้อง คลื่นไส้ อาเจียน ถ่ายเหลว

หากมีอาการดังกล่าวที่รุนแรงเฉียบพลัน อาการมากกว่าหรือเท่ากับ 2 ข้อ ให้โทรแจ้งสายด่วนฉุกเฉิน 1669 และแพทย์ผู้ทำวิจัย หรือหากอาการยังไม่รุนแรง สามารถโทรปรึกษาแพทย์ผู้ทำวิจัยได้

สายด่วนฉุกเฉิน
1669

แพทย์ผู้ทำวิจัย
แพทย์หญิง ชวลี เชื้อขวลิต
เบอร์โทร. 0611956493,
0922652416



CURRICULUM VITAE

CURRICULUM VITAE

NAME Chawalee Chueachavalit

EDUCATIONAL BACKGROUND

2014 Doctor of Medicine degree from Our Lady of Fatima University, College of Medicine

2008 Bachelor of Science in Chemistry Pre-Medicine from Wichita State University

WORK EXPERIENCE

2017-Present General Practitioner
Aesthetic Doctor

2015-2016 Internship
Lerdsin Hospital

2014-2015 Externship
Nopparatrajathanee Hospital

PUBLICATION

Talaty, E. R., Chueachavalit, C., Osburn, S., & Van Stipdonk, M. J. (2007).

Investigation of the neutral loss of a full amino acid mass during collision-induced dissociation of the b ion derived from a model peptide containing a 4-aminobutyric acid residue. *Rapid Communications in Mass Spectrometry: An International Journal Devoted to the Rapid Dissemination of Up-to-the-Minute Research in Mass Spectrometry*, 21(15), 2529-2537.