EFFICACY AND SAFETY OF MOISTURIZER CONTAINING 5% PANTHENOL, MADECASSOSIDE, AND COPPER-ZINC-MANGANESE VERSUS 0.02% TRIAMCINOLONE ACETONIDE CREAM IN DECREASING ADVERSE REACTION AND DOWNTIME AFTER ABLATIVE FRACTIONAL CARBON DIOXIDE LASER RESURFACING

BY

MISTER APHINUT SRITURAVANIT

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE (DERMATOLOGY)

CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE

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was approved as partial fulfillment of the requirements for
the degree of Master of Science (Dermatology)
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Thesis Title	EFFICACY AND SAFETY OF MOISTURIZER CONTAINING 5% PANTHENOL, MADECASSOSIDE, AND COPPER-ZINC-MANGANESE VERSUS 0.02% TRIAMCINOLONE ACETONIDE CREAM IN DECREASING ADVERSE REACTION AND DOWNTIME AFTER ABLATIVE FRACTIONAL CARBON DIOXIDE LASER RESURFACING
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ABSTRACT

Fractional carbon dioxide ($FrCO_2$) laser is effective for atrophic acne scar treatment but the downtime following this procedure is unavoidable. Postoperative topical steroid decreases the risk of this downtime, but in the meantime increases other side effects. The objective of this study was to evaluate the clinical efficacy and safety of the moisturizer containing anti-inflammatory ingredients including 5% panthenol, madecassoside, and copper-zinc-manganese (experimental cream) versus 0.02% Triamcinolone acetonide (TA) cream to improve wound healing and decrease adverse effects and downtime after $FrCO_2$ laser treatment in acne scar. We conducted a double-blind, split face, randomized controlled trial in 20 subjects, with $FrCO_2$ laser treatment on both sides of their faces, and randomly treated with these 2 post-treatment regimens on each side of the face for 7 days. We evaluated the result by using the questionnaires, the expert panel assessment of the photography, downtime

and side effects evaluated by subjects, and facial scanning by the Antera 3D device. The result revealed that both the experimental cream and 0.02% TA cream significantly decreased post-laser downtime including swelling, redness, crusting and scaling in 5-7 days. Moreover, they produced lower of the PIH incidence when compared with petrolatum from the previous study. There was no significant different of the efficacies to decrease downtime between the experimental cream and the 0.02% TA cream. Hence, the moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese yielded comparable efficacies to 0.02% TA cream for the improvement of wound healing, decreased adverse reactions and downtime after $FrCO_2$ laser irradiation. This moisturizer could be a novel treatment modality for the reduction of post-ablative laser downtime by using non-steroidal anti-inflammatory agents in a bid to avoid adverse effects from steroids and improve wound healing process.

Keywords: Panthenol, Madecassoside, Copper-Zinc-Manganese, Fractional ablative laser, Downtime

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Mr. Aphinut Srituravanit

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LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
$FrCO_2$	Fractional carbon dioxide
AFR	Ablative fractional laser resurfacing
FP	Fractional photothermolysis
CO_2	Carbon dioxide
MTZs	Microscopic treatment zones
PIH	Post inflammatory hyperpigmentation
SPT	Skin phototype
TEWL	Transepidermal water loss
SPF	Sun protection factor
UV	Ultraviolet
TA	Triamcinolone acetonide
HQ	Hydroquinone
RA	Retinoic acid
UVB	Ultraviolet-B
UVA	Ultraviolet-A
COX-2	Cyclooxygenase-2
PG	Prostaglandin
SOD	Superoxide dismutase
CuZnSOD	Copper-zinc superoxide dismutase
MnSOD	Manganese superoxide dismutase
CAT	Catalase
NAFR	Non-ablative fractional laser resurfacing
TCA CROSS	Trichloroacetic acid chemical reconstruction of skin scars
S/E	Side effect
SCORAD	Scoring atopic dermatitis
SCOREPI	Score de Reparation de l'Epiderme

KFs	Keloid fibroblasts
OPD	Outpatient department
TTMH	Thailand tobacco monopoly hospital
DQLI	Dermatology quality of life index
N	Number
AHA	Alpha hydroxyl acid
Vit.A	Vitamin A
IPL	Intense pulsed light
Qs Nd:Yag	Q-switched neodymium-doped yttrium aluminum garnet
RF	Radiofrequency
Botox	Botulinum toxin
EC	Experimental cream
3D	Three dimension
PA	Protection grade of ultraviolet A
CP	0.05% Clobetasol propionate
PT	Petrolatum
ACD	Allergic contact dermatitis
CICM	Chulabhorn international college of medicine

CHAPTER 1
INTRODUCTION

1.1 Fractional carbon dioxide laser

1.1.1 Principle

Fractional carbon dioxide ($FrCO_2$) is one type of the ablative fractional laser resurfacing (AFR) which is based on the principle of fractional photothermolysis (FP). This type of laser was created by combining the 10,600 nm wavelength of the carbon dioxide (CO_2) laser with an FP system. It produces controlled dermal coagulation extending to far greater depths than traditional CO_2 laser and non-ablative devices. This laser ablates epidermis and heats dermal tissue by creating multiple zones of microthermal injury within the treatment area, called microscopic treatment zones (MTZs). The MTZs are multiple sharply columnar tissue denaturations with a diameter of about 100 μm that is surrounded by normal tissue. This microscopic pattern promotes greater tissue contraction, collagen production and collagen remodeling (1).

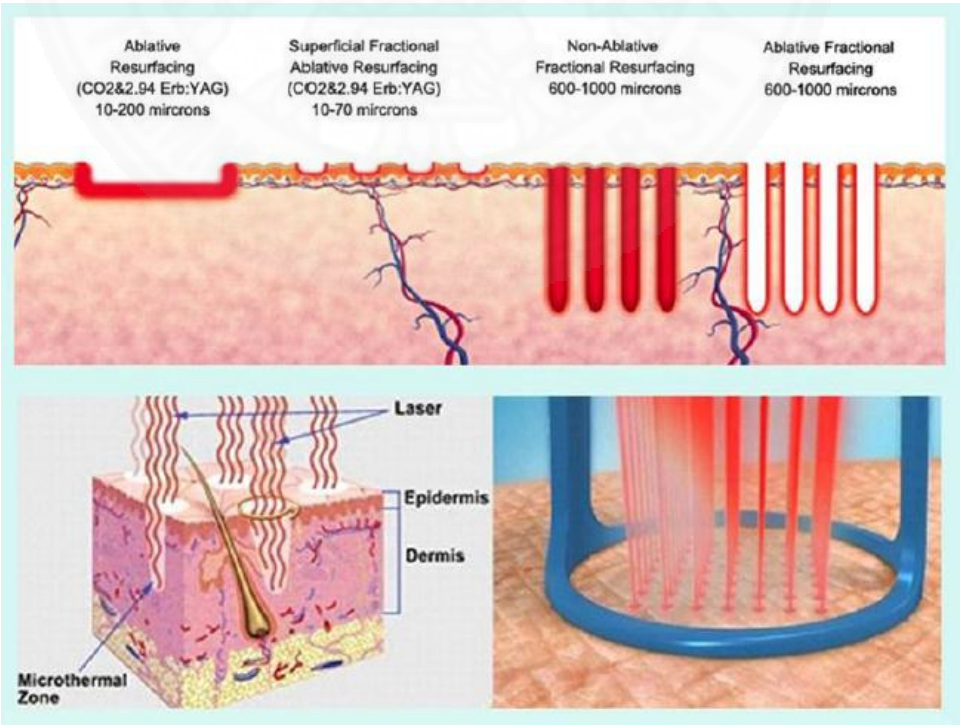


Figure 1.1 MTZs pattern of ablative fractional laser resurfacing (2)

1.1.2 Downtime

This laser is an effective tool for atrophic acne scar treatment (3). However, the downtime following this procedure is often unavoidable. Post inflammatory hyperpigmentation (PIH) is the most common adverse effect, especially in dark-skin individuals including most Asian. The incidence of PIH following AFR in patients with skin phototype (SPT) IV is as high as 92% (4). In details, this downtime includes white frosting which may last for 5 to 10 minutes immediately after laser irradiation, followed by erythema and edema that usually persist for 24 to 72 hours. Normally, superficial crusting occurs and re-epithelialization is complete in 5 to 7 days depend on the density and the energy of the laser. PIH can be observed after the crusts slough off, normally at around 1 or 2 weeks after the procedure (3).

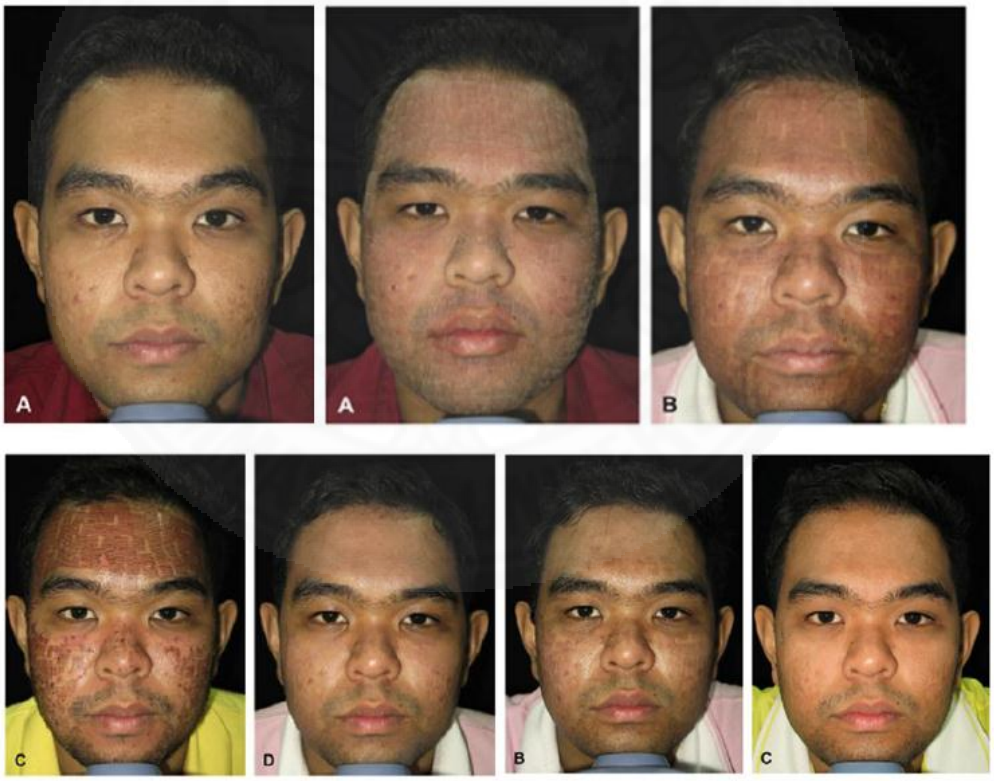


Figure 1.2 Downtime in a Thai patient who underwent $FrCO_2$ (3)

1.1.3 Treatment modalities of the laser downtime

1.1.3.1 Moisturizer

Moisturizer plays a crucial role in the wound healing and skin barrier repairing process. Occlusive moisturizer acts as a barrier to prevent skin from insensible water loss. This type of moisturizer coats the stratum corneum, decreases transepidermal water loss (TEWL), and provides an emollient effect (5). Petrolatum, for example, can decrease abundant of TEWL but it also has a greasy feeling that may unacceptable to some patients.

1.1.3.2 Sun avoidance and sun protection

Photoprotection is an integral part in the treatment of PIH including those caused by $FrCO_2$. Patients should be educated to use sunscreen with the sun protection factor (SPF) at least 30 and sun-protective measures, such as avoidance and protective clothing (6). Sunlight can worsen PIH via ultraviolet (UV)-induce melanogenesis pathway.

1.1.3.3 Topical steroid

Topical steroid is well-known for its anti-inflammatory effect. This drug is used for the treatment of many inflammatory skin diseases. However, side effects are observed when it is used in high potency or long duration. The side effects include atrophic changes, acneiform eruption, pigmentary changes, development of infection, and allergic reaction (7). In the recent study, 2 from 40 patients developed acneiform eruption caused by 2 days applying of 0.05% Clobetasol propionate after undergoing $FrCO_2$ laser (8).

1.1.3.4 Whitening agents

Many whitening agents improve PIH including those caused by $FrCO_2$. The current drugs include hydroquinone (HQ), retinoic acid (RA), azelaic acid, kojic acid, arbutin, niacinamide, N-acetyl cysteine (NAC), ascorbic acid, licorice, and soy (9). Kligman solution is the combination of HQ, RA, and steroid, which is widely used for PIH treatment due to its significant result. However, high concentration or chronic using of HQ may result in side effects such as, hypopigmentation, and ochronosis.

1.2 The experimental cream

The moisturizer containing 5% panthenol, madecassoside, and copper – zinc – manganese (Cicaplast Baume B5, La Roche-Posay, France) is the soothing cream used for normal and sensitive skin irritations. This product can be applied to body, face and lips. Moreover, it can be used in any ages including babies, and is well-tolerated for most people. Besides, this moisturizer containing anti-inflammatory ingredients is found effective for a treatment of various skin conditions such as atopic dermatitis, irritative dermatitis, xerosis, and cheilitis (10, 11). Three active ingredients in this product have been studied for their positive effect in wound healing and anti-inflammatory property.

Figure 1.3 Cicaplast Baume B5, La Roche-Posay, France (12)

Table 1.1 Active ingredients in the experimental cream and their positive effects

Dexpanthenol	stable alcoholic form of vitamin B5	improve skin barrier by decreasing TEWL, maintaining skin softness, activating fibroblast proliferation, and providing anti-inflammatory effect
Madecassoside	extract from Centella asiatica	induce collagen expression, modulate inflammatory mediators, prevent aging, and inhibit proliferation of keloid fibroblast
Copper - Zinc – Manganese,	the trace elements	have healing properties and anti-oxidant effect

1.2.1 Active Ingredient

1.2.1.1 Dexpanthenol

Dexpanthenol (panthenol) is the active alcoholic form of pantothenic acid. It is a pro-vitamin B-complex composed in a normal component of skin and hair. Normally, topical dexpanthenol is converted to pantothenic acid which is a component of coenzyme A that is essential for the lipid bilayer synthesis in the stratum corneum. Dexpanthenol is known to improve skin barrier function by decreasing TEWL, maintaining skin softness, activating fibroblast proliferation, and providing anti-inflammatory effect (13). Recent studies found that topical dexpanthenol is useful for the wound healing in burns, fissures, corneal lesions, and allergic dermatitis. In addition, it has minimal risks of skin irritancy, and is well tolerated for most people.

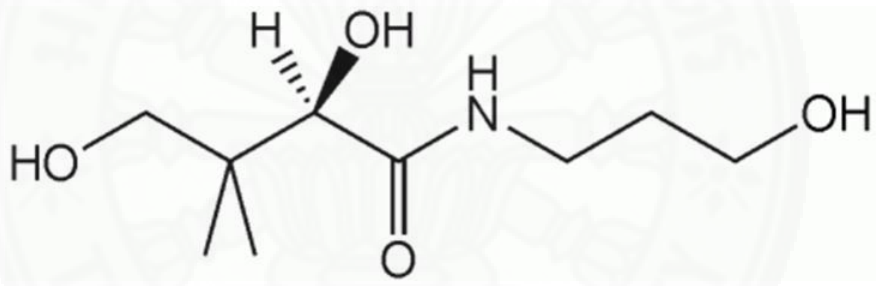


Figure 1.4 Structure of dexpanthenol (14)

1.2.1.2 Madecassoside

Madecassoside is one of the extracts isolated from Centella asiatica. It has various positive effects including wound healing boosting, anti-inflammatory, anti-aging activities, and protective effects against oxidative stress and ultraviolet-B (UVB) radiation (15, 16). In details, it decreases inflammatory activity by inhibiting of Cyclooxygenase-2 (COX-2) and prostaglandin (PG) production.

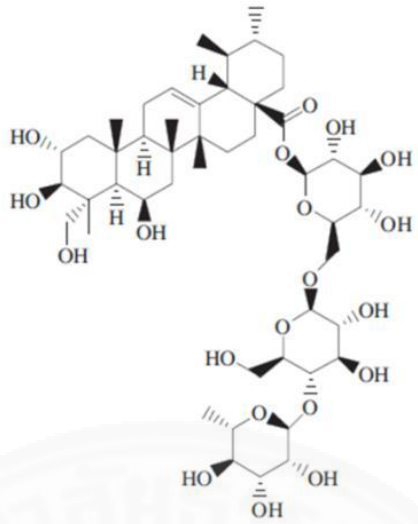


Figure 1.5 Structure of madecassoside (17)

1.2.1.3 Copper-Zinc-Manganese

The trace elements copper, zinc and manganese are the component of the skin's enzymatic antioxidant defense, which includes copper-zinc superoxide dismutase (CuZnSOD), manganese superoxide dismutase (MnSOD) and catalase (CAT). These enzymes are known to maintain a balance within cells and regulate the antioxidant defense system during intrinsic aging and photoaging processes (18).

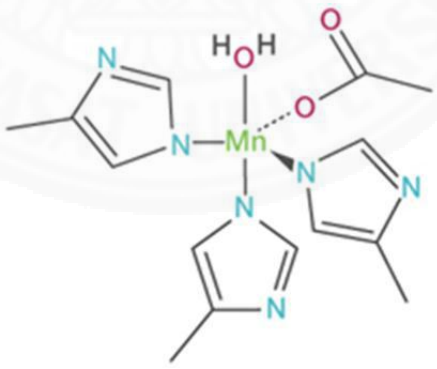


Figure 1.6 Structure of manganese superoxide dismutase (MnSOD) (19)

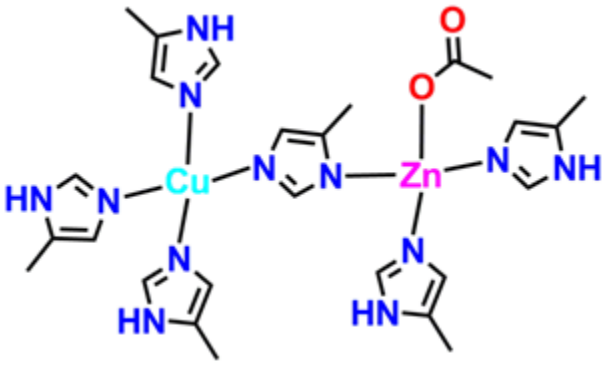


Figure 1.7 Structure of copper-zinc superoxide dismutase (CuZnSOD) (20)

1.3 0.02% Triamcinolone acetonide

Topical glucocorticoids are highly effective in many inflammatory skin diseases, and few side effects are observed when a low-potency preparation is used for short period of time. However, the use of this drug in high potency or long duration increases risk of the following adverse effects; atrophic changes, acneiform eruption, pigmentary changes, development of infection, and allergic reaction (7). In the recent study, 2 from 40 patients developed acneiform eruption after applied 0.05% Clobetasol propionate twice daily for 2 days after $FrCO_2$ laser procedure (8). 0.02% triamcinolone acetonide (TA) is mild to moderate potent steroid. It is categorized in class 6 for the glucocorticoid potency classification, and is classified in the structural class B for the cross-reactivity classification (21) which mean, this strength of topical steroid is unlikely to cause allergic reaction. This drug is well-known for its anti-inflammatory property and is one of the main treatment modalities for various inflammatory skin conditions such as atopic dermatitis.

Table 1.2 Glucocorticoid potency classification and its commonly used (21)

POTENCY RANKING OF SOME COMMONLY USED TOPICAL GLUCOCORTICOSTEROIDS

CLASS 1 (SUPERPOTENT)

- Clobetasol propionate gel, ointment, cream, lotion, foam, spray and shampoo 0.05%
- Betamethasone dipropionate gel* and ointment* 0.05%
- Diflorasone diacetate ointment* 0.05%
- Fluocinonide cream 0.1%
- Flurandrenolide tape 4 mcg/cm²
- Halobetasol propionate ointment and cream 0.05%

CLASS 2 (HIGH POTENCY)

- Amcinonide ointment 0.1%
- Betamethasone dipropionate cream*, lotion*, gel and ointment 0.05%
- Clobetasol propionate solution ("scalp application") 0.05%
- Desoximetasone ointment and cream 0.25% and gel 0.05%
- Diflorasone diacetate ointment and cream* 0.05%
- Fluocinonide gel, ointment, cream and solution 0.05%
- Halcinonide ointment, cream and solution 0.1%
- Mometasone furoate ointment 0.1%
- Triamcinolone acetonide ointment 0.5%

CLASS 3 (HIGH POTENCY)

- Amcinonide cream and lotion 0.1%
- Betamethasone dipropionate cream and lotion 0.05%
- Betamethasone valerate ointment 0.1%
- Diflorasone diacetate cream 0.05%
- Fluticasone propionate ointment 0.005%
- Triamcinolone acetonide ointment 0.1% and cream 0.5%

CLASS 4 (MEDIUM POTENCY)

- Betamethasone valerate foam 0.12%
- Desoximetasone cream 0.05%
- Fluocinolone acetonide ointment 0.025%
- Flurandrenolide ointment 0.05%
- Hydrocortisone valerate ointment 0.2%
- Mometasone furoate cream and lotion 0.1%
- Triamcinolone acetonide ointment (Kenalog®) and cream 0.1% or spray 0.2%

CLASS 5 (MEDIUM POTENCY)

- Betamethasone dipropionate lotion 0.05%
- Betamethasone valerate cream and lotion 0.1%
- Clocortolone pivalate cream 0.1%
- Fluocinolone acetonide cream 0.025% or oil and shampoo 0.01%
- Fluticasone propionate cream and lotion 0.05%
- Flurandrenolide cream and lotion 0.05%
- Hydrocortisone butyrate ointment, cream and lotion 0.1%
- Hydrocortisone probutate cream 0.1%
- Hydrocortisone valerate cream 0.2%
- Prednicarbate ointment and cream 0.1%
- Triamcinolone acetonide ointment 0.025% and lotion 0.1%

CLASS 6 (LOW POTENCY)

- Alclometasone dipropionate ointment and cream 0.05%
- Triamcinolone acetonide cream 0.1% (Aristocort®)
- Betamethasone valerate lotion 0.1%
- Desonide gel, ointment, cream, lotion and foam 0.05%
- Fluocinolone acetonide cream and solution 0.01%
- Triamcinolone acetonide cream and lotion 0.025%

CLASS 7 (LOW POTENCY)

- Topicals with hydrocortisone, dexamethasone and prednisolone

*Optimized vehicle.

Table 1.3 Classification of corticosteroid by cross-reactivity (7)

Classification of Corticosteroids by Cross-Reactivity

Structural Class	A	B	C	D1	D2
Type	Hydrocortisone	Triamcinolone Acetonide	Betamethasone	Betamethasone dipropionate	Methylprednisolone aceponate
Structure	C16-no methyl substitution Probable C21-short chain ester		C16 methyl substitution	C16 methyl substitution C17/21 long chain ester	C16-no methyl substitution, no halogenation
Cross-reactions	Cross-reacts with D2	Budesonide specifically cross-reacts with D2			Cross-reacts with A and budesonide
Patch-test substance	Tixocortol-21-pivalate	Budesonide Triamcinolone acetonide		Clobetasol-17-propionate	Hydrocortisone-17-butyrate

Table 1.4 Therapeutic modalities for atopic dermatitis (22)

THERAPEUTIC LADDER FOR ATOPIC DERMATITIS	Evidence
Emollients (basic therapy)	1
Topical corticosteroids	1
Topical calcineurin inhibitors	1
UVB (narrowband>broadband), UVA-UVB, UVA1 or oral PUVA	1
Systemic corticosteroids (short term for severe acute flares; "rebound" exacerbations often occur upon discontinuation)	2
Cyclosporine (short/intermediate term)	1
Azathioprine	1
Mycophenolate mofetil/enteric-coated mycophenolate sodium	1*/2
Methotrexate	1*/2
Interferon-γ	**
IVIg	2†
Omalizumab	2†
Rituximab	2
Other (crude coal tar, hydroxychloroquine, extracorporeal photochemotherapy)	2–3

1.4 Conceptual Framework

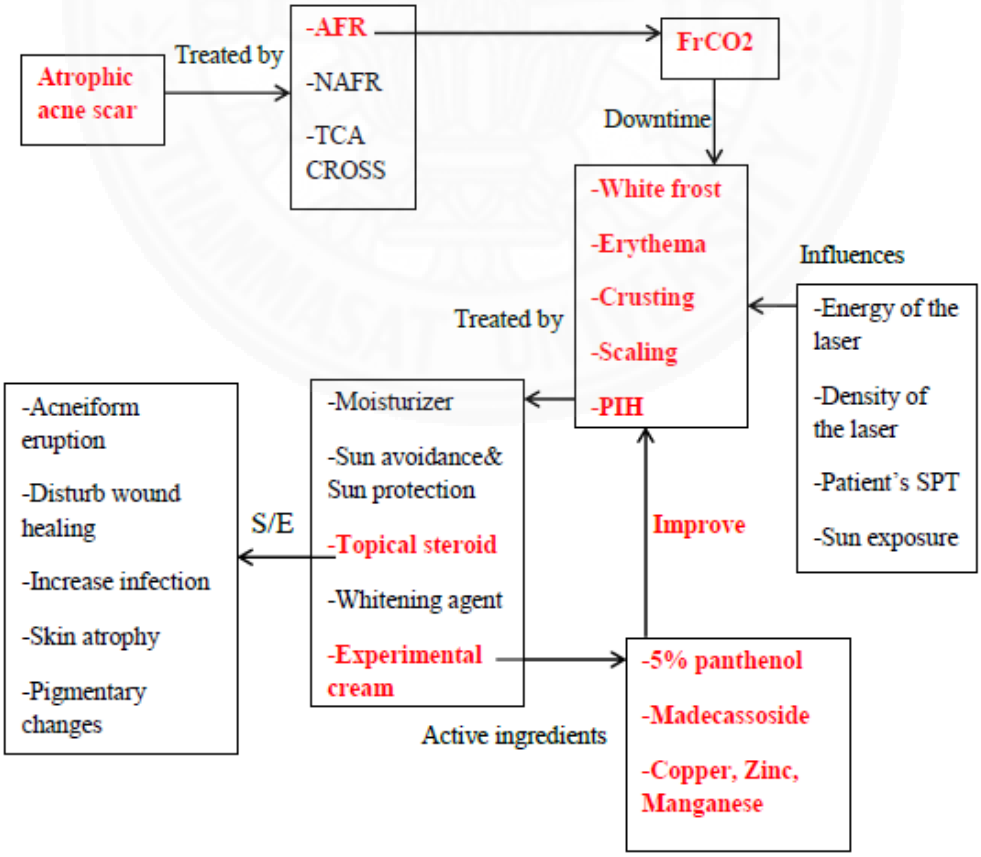


Figure 1.8 Conceptual framework

1.5 Significance of the research

This moisturizer containing anti-inflammatory ingredients could be a novel treatment modality for the reduction of post-ablative laser downtime by using non-steroidal anti-inflammatory agents in a bid to avoid adverse effects from steroids and improve wound healing process.

CHAPTER 2
REVIEW OF LITERATURE

2.1 Fractional carbon dioxide laser

In 2007, Chan et al. studied the prevalence and risk factors of PIH that were associated with the use of fractional laser resurfacing in Asians. The result came out that both the density and the energy of the treatment determined the risk of PIH in dark-skin patients (23).

In 2009, Cho et al. studied the efficacy and safety of the 10,600-nm ablative CO_2 fractional laser in the treatment of acne scars in Korean patients. They concluded that the laser promised to be an effective tool in the technologies for the acne scar treatment, and the side effect he found was only post-treatment erythema (24).

In 2010, Manuskiatti et al. evaluated the efficacy and safety of carbon-dioxide ablative fractional resurfacing on atrophic acne scars in Asian individuals. They found that the laser appeared to be effective and well tolerated for the treatment of atrophic acne scars in Asians, but mild PIH was found to be the side effect, that was happened as high as 92% of the subject (3).

In 2011, Shamsaldeen el al. studied the rate of the adverse events associated with the use of $FrCO_2$. They found that most common post-operative side effect was acneiform eruption. PIH was found in just few cases. However, the study was conducted on the individual with SPT I-II (fair skin color) only (25).

In 2014, Wanitphakdeedecha et al. studied whether the use of broad-spectrum sunscreen with anti-inflammatory agents starting on the first day after $FrCO_2$ reduced the incidence of post laser PIH. They found that the regimen decreased the incidence of PIH after laser treatment at 1-week postoperatively (26).

In 2015, Cheyasak et al. investigated the effect of short-term application of high potency topical corticosteroids on the incidence of PIH after ablative fractional resurfacing in Asians. They found that short course (2 days) of topical 0.05% Clobetasol propionate decreased the risk of PIH after ablative fractional resurfacing. However, this high potency steroid may disturb the wound healing

process and increase the risk of post-operative infection. 2 subjects who had got the steroid treatment post-operatively later developed acneiform eruption on the steroid treated side (8).

In conclusion, $FrCO_2$ is an effective treatment for atrophic acne scar. However, after undergoing $FrCO_2$, most patients have to anticipate the downtime including white frosting which may last for 5 to 10 minutes immediately after laser irradiation, followed by erythema and edema that usually persist for 24 to 72 hours. Normally, superficial crusting occurs and re-epithelialization is complete in 5 to 7 days depend on density and energy of the laser. PIH can be observed after the crusts slough off, normally at around 1 or 2 weeks after the procedure.

2.2 The experimental cream

In 2012, Seite et al. investigated this product containing 0.3% madecassoside on mild to moderate atopic dermatitis children in a randomized, double-blind, placebo-controlled trial. They found that this product decreased scoring atopic dermatitis (SCORAD), pruritus symptom, and loss of sleep significantly, when compared to the placebo (11).

Table 2.1 SCORAD in the group treated with 0.3% madecassoside and the placebo from day 0 to day 84 (11)

In the group treated with 0.3% madecassoside containing ointment a decreased SCORAD by 30% and 53% was noticed at D42 and D84 respectively (p<0.01 as compared to placebo group).

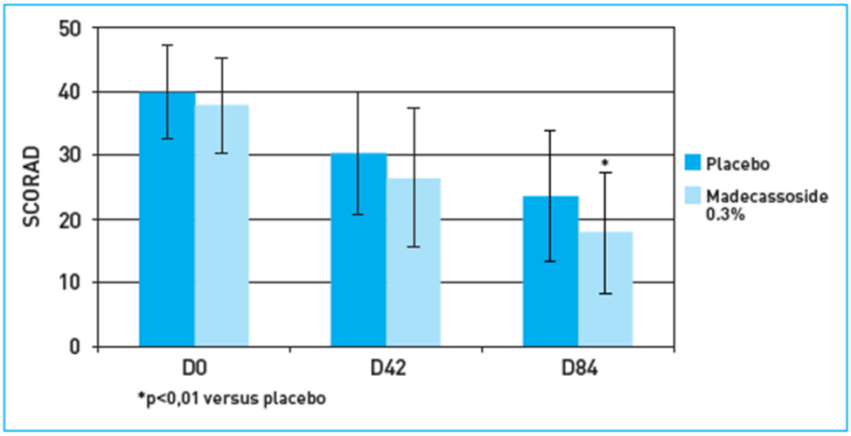


Table 2.2 Pruritus symptom in the group treated with 0.3% madecassoside and the placebo from day 0 to day 84 (11)

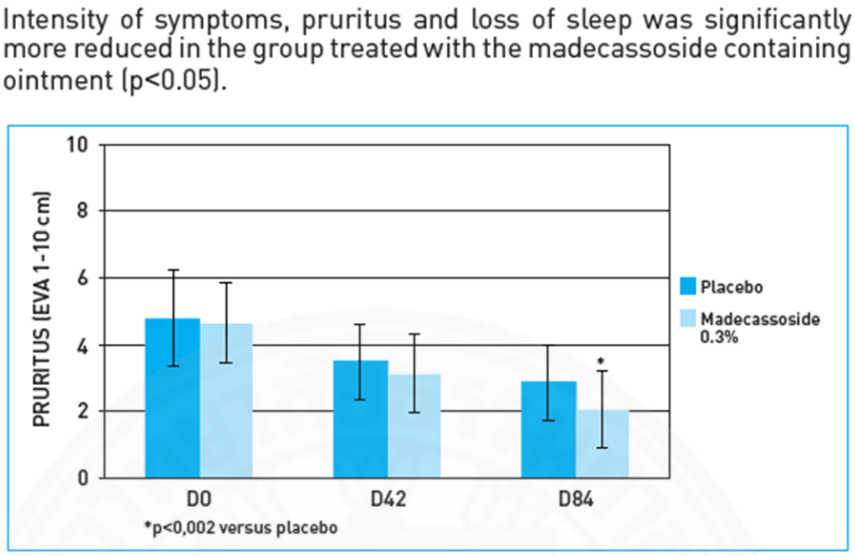
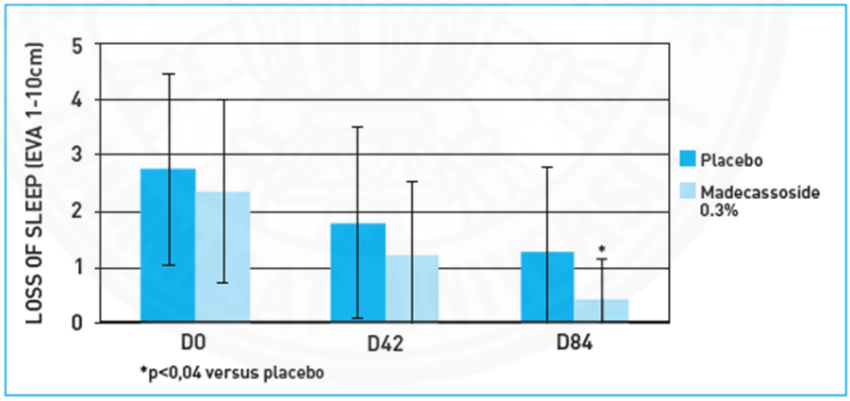


Table 2.3 Loss of sleep symptom in the group treated with 0.3% madecassoside and the placebo from day 0 to day 84 (11)



In 2012, Crickx et al. conducted an observational study on 2,440 patients. They observed the use of this product prescribed by 313 dermatologists and 99 pediatricians. They found that the product decreased the symptom of burning, tingling, pain, and itching sensation significantly on day 22 compared to day 0. Moreover, the product was prescribed by many dermatologists in order to treat various skin conditions including atopic dermatitis, irritative dermatitis, xerosis, cheilitis, and many others (10).

In 2013, Le Maitre et al. created an epidermal repair score called “Score de Reparation de l’Epiderme” (SCOREPI) to assess skin deterioration in irritative dermatitis before and after the use of this product. They found that the SCOREPI was reproducible, easy to use, and sensitive to change. This product also improved this score significantly (27).

2.3 Dexpanthenol

In 2002, Proksch et al. studied the effects of dexpenthenol containing cream on skin barrier repair, stratum corneum hydration, skin roughness, and inflammation. They found that the cream produced significantly enhanced skin barrier repair and stratum corneum hydration, while reduced skin roughness and inflammation (28).

In 2002, Ebner et al. studied the topical use of dexpanthenol in skin disorders. They found that dexpanthenol could be used to treat many skin disorders which are; skin abrasion, chronic ulcer, decubital ulcer, anal fissure, non-severe burn, diaper dermatitis, and radiation dermatitis (13).

In 2003, Biro et al. investigated the efficacy of dexpanthenol in skin protection against irritation in a randomized, prospective, double-blind, placebo-controlled study. They found that dexpanthenol had the protective effect against skin irritation, by which skin hydration was found to be most useful in monitoring the effects (29).

In 2011, Camargo et al. evaluated the skin moisturizing efficacy of formulations containing different concentrations of panthenol. They found that panthenol-based formulations increased skin moisture significantly and had an effect on skin barrier function by decreasing TEWL (30).

In 2012, Heise et al. studied the effect of dexpanthenol to the gene expression in skin wound healing. They found that upregulation of IL-6, IL-1, CYP1B1, CXCL1, CCL18 and KAP 4–2 gene expression and downregulation of psorasin mRNA and protein expression were identified in samples treated topically with dexpanthenol. They concluded that this founding was helped to confirm that dexpanthenol was effective for improving wound healing (31).

In conclusion, dexpanthenol has the property of:

a. Moisturizer

b. Decreasing TEWL

c. Maintaining skin softness and elasticity

d. Activating fibroblast proliferation

e. Stimulating re-epithelization

f. Anti-inflammatory

2.4 Madecassoside

In 2008, Haftek et al. studied long-term effects of a topical treatment with ascorbic acid and madecassoside in photoaged human skin. They found that two-thirds of the subjects showed an improvement in the wrinkle, firmness, roughness, and skin hydration (15).

In 2010, Song et al. studied the effects of madecassoside on the proliferation and apoptosis of keloid fibroblasts (KFs). They found that madecassoside inhibited the proliferation of KFs in a time and concentration dependent manner, and induced KF apoptosis. Moreover, they found that madecassoside induced the apoptosis of KFs through a mitochondrial-dependent pathway. They concluded that madecassoside induced apoptosis of keloid fibroblasts via a mitochondrial-dependent pathway without disturbing normal fibroblast (16).

In 2011, Song et al. studied the potential of madecassoside on the migration of KFs and its mechanism. They found that madecassoside was shown to remarkably attenuate the phosphorylation of cofilin, p38 MAPK and phosphatidylinositol-3-kinase (PI3K)/AKT signaling. They concluded that madecassoside could be useful in the treatment and/or prevention of hypertrophic scars and keloids (32).

In 2013, Jung et al. investigated the effects of madecassoside on ultraviolet (UV)-induced melanogenesis and mechanisms in a co-culture system of keratinocytes and melanocytes. They found that madecassoside significantly reduced UV-induced melanin index at 8 weeks after topical application. They concluded that

madecassoside has an effect to inhibit hyperpigmentation caused by UV irradiation (33).

In conclusion, madecassoside has the property of:

a. Inducing collagen expression

b. Modulating inflammatory mediator

c. Preventing aging

d. Inhibiting proliferation and migration of keloid fibroblast

e. Wound healing boosting

f. Inhibiting melanin synthesis

g. Promoting re-epithilization

2.5 Copper-Zinc-Manganese

In 1999, Tenaud et al. demonstrated how the expressions of integrins in keratinocyte were modulated in vitro by trace elements (copper-zinc-manganese). They found that zinc, copper and manganese gluconates enhanced a6 (one of the integrins) expression, thus favored migration and dermal–epidermal adhesion (34).

In 2000, Takahashi et al. investigated the role of Superoxide dismutase (SOD) in the ultraviolet B (UVB) irradiation-induced apoptosis. They found that copper, zinc–superoxide dismutase could protect skin from ultraviolet B-induced apoptosis of SV40-transformed human keratinocytes, and the protection was associated with the increased levels of antioxidant enzymes (35).

In 2000, Sasaki et al. examined the possible role of endogenous copper, zinc-superoxide dismutase or manganese-superoxide dismutase against UVB-induce reactive-oxygen-species-mediated keratinocyte injury in vitro. They found that endogenous copper, zinc-superoxide dismutase might play a primary protective role against UVB-induce injury of the human keratinocyte cell line HaCaT (36).

In 2002, Sander et al. hypothesized that chronic and acute photodamage is mediated by depleted antioxidant enzyme (catalase, copper-zinc superoxide dismutase, and manganese superoxide dismutase) expression and increased oxidative protein modifications. They found that depleted antioxidant enzyme expression in photodamaged skin was associated with higher levels of protein oxidation (18).

In 2009, Demertzi et al. studied in vitro and in vivo anti-inflammatory activity and anti-proliferative activity of mefenamic acid and its metal complexes with manganese, cobalt, nickel, copper and zinc. They concluded that this complexes of mefenamic acid [Mn(mef)2(H2O)2], [Co(mef)2(H2O)2], [Ni(mef)2(H2O)2], [Cu(mef)2 (H2O)]2 and [Zn(mef)2] had the antioxidant ability and might prove useful for treating a variety of inflammatory diseases, led to the development of new drugs (37).

In conclusion, copper-zinc-manganese has the property of:

a. Providing antioxidant effect

b. Preventing aging

c. Controlling dermal-epidermal adhesion

d. Protecting from UVB

e. Regulates epidermal proliferation

f. Controlling the proliferation of keratinocytes and fibroblasts in the skin

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Objectives

3.1.1 Primary objective

To evaluate the clinical efficacy and safety of moisturizer containing anti-inflammatory ingredients vs 0.02% TA cream for improving wound healing and decreasing adverse reactions and downtime after $FrCO_2$ resurfacing

3.1.2 Secondary objectives

3.1.2.1 To evaluate the clinical efficacy and safety of moisturizer containing anti-inflammatory ingredients vs 0.02% TA cream for reducing PIH after $FrCO_2$ resurfacing.

3.1.2.2 To compare the laser treatment result when performing with different post treatment regimens including the moisturizer containing anti-inflammatory ingredients and 0.02% TA cream.

3.2 Study design

Interventional: Therapeutic trial, a prospective, double-blinded, split face, randomized control trial

3.3 Target population

Patient aged ≥18 years with atrophic facial acne scars on both cheeks for at least 6 months who attended the outpatient department (OPD) at Thailand Tobacco Monopoly Hospital (TTMH).

3.4 Selection criteria

3.4.1 Inclusion criteria

3.4.1.1 Male or female aged ≥18 years

3.4.1.2 Had atrophic facial acne scars on both cheeks for at least 6 months

3.4.2 Exclusion criteria

3.4.2.1 Pregnancy and those who intended to get pregnant within 2 months

3.4.2.2 Lactating mother

3.4.2.3 Skin infections, inflamed acne or photosensitive dermatoses

3.4.2.4 Concomitant treatment to the involved skin areas

3.4.2.5 Propensity for keloid scarring

3.4.2.6 Received isotretinoin, underwent filler injections or ablative/nonablative laser skin resurfacing procedures within the preceding 3 months

3.4.2.7 Use of a systemic retinoid or steroid within 6 months before study initiation

3.4.2.8 History of herpes viral infection

3.4.2.9 Allergy to Triamcinolone acetonide, dexpanthenol, or madecassoside

3.4.2.10 Presence of evidence indicating likely poor compliance with the protocol

3.4.3 Discontinuation criteria

3.4.3.1 Patient who had got pregnant during the protocol

3.4.3.2 Patient who was unwilling to continue participating in the study

3.5 Sample size

Sample size = 20 (At least 18 from the statistical calculation), Effect size = 0.3, Alpha error = 0.05, Power = 0.9, Number of groups = 2, Number of measurements = 8. The sample size calculation formula is as following;

$$F \text{ tests} \quad \mu_{ij} - \mu_i - \ldots \quad f = \frac{\sigma_\mu}{\sigma}$$
$$\mu_j + \mu = 0$$
$$i = 1, \ldots, k$$
$$j = 1, \ldots, m$$

Figure 3.1 Sample size calculation formula

3.6 Recruitment process

We used the invitation poster to persuade the volunteers. These posters contained important details of the study in brief and placed around TTMH hospital.

3.7 Preparation of research subjects

3.7.1 Subjects were selected to enroll in the study according to the selection criteria.

3.7.2 Details in the information sheet were informed to all subjects.

3.7.3 The subjects signed an inform consent form for participation in the study. Those who asked for subject's consent was a nurse or an investigator's staff who had no benefit from the study. The process to inform the details was by describing all details to subjects and let them read information sheet by themselves before signing in the study. The place for informed consent was the TTMH hospital. For the blind or incapable volunteers, relative or someone who had no benefit from the study was responsible to inform all the studies 'details before informed consent. When the volunteers decided to join the study, they must sign in by pumping their fingerprint with inerasable ink followed by signing from their witness.

The investigator had kept one informed consent document and gave another one to the subjects during the study period.

3.7.4 The important information such as subject's demographic data was recorded after signing in.

3.8 Treatment

3.8.1 Preoperative care

Preoperatively, all participants were instructed to clean their face with the sensitive facial liquid cleanser. After that, Lidocaine 2.5% and prilocaine 2.5% cream (Emla cream 5%; a eutectic mixture of local anesthetic, AstraZeneca LP, Wilmington, DE) was applied under occlusion for 45 minutes.

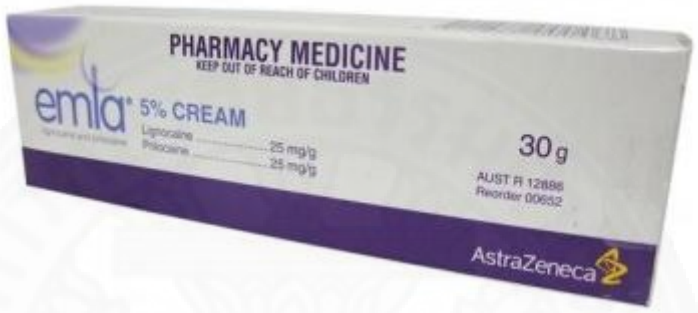


Figure 3.2 Emla cream 5%; Lidocaine 2.5% and prilocaine 2.5% cream (38)

3.8.2 Intervention

All participants then underwent $FrCO_2$ laser irridiation (eCO_2; Lutronic Co., Ltd, South Korea) on both cheeks by a single physician following these parameters of static mode: 120 μm beam size, 30 w peak power, 50 mj pulse energy, 1 mm ablation depth, with 2 passes of 100 spots/cm^2 density and less than 15% coverage. Besides, no concurrent use of epidermal cooling device was performed during the procedure. No postoperative analgesic treatment was required beyond the application of ice compresses for approximately 15–20 min. No prophylactic antibiotics or antivirals were given to any patients.

Figure 3.3 The eCO2 fractional laser (39)

3.8.3 Postoperative care

Immediately after the laser irradiation, all subjects were taken high-resolution camera images of their face in 5 positions, with facial scanning by Antera device (Antera 3D; Miravex Co., Ltd, Dublin, Republic of Ireland) before allowed for ice compression. Two sides of each patient's face were randomly treated with 2 different post-treatment agents; one side of the face with the experimental cream (moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese) twice daily for 7 days, while another side with 0.02% TA cream twice daily for 7 days. All subjects must use 2 separated cotton-buds for applying each cream to avoid contamination. Moreover, they were instructed to wear a broad-spectrum sunscreen with a sun protection factor of 40, avoid sun exposure, and avoid using of any topical preparations on the face during the period of study.

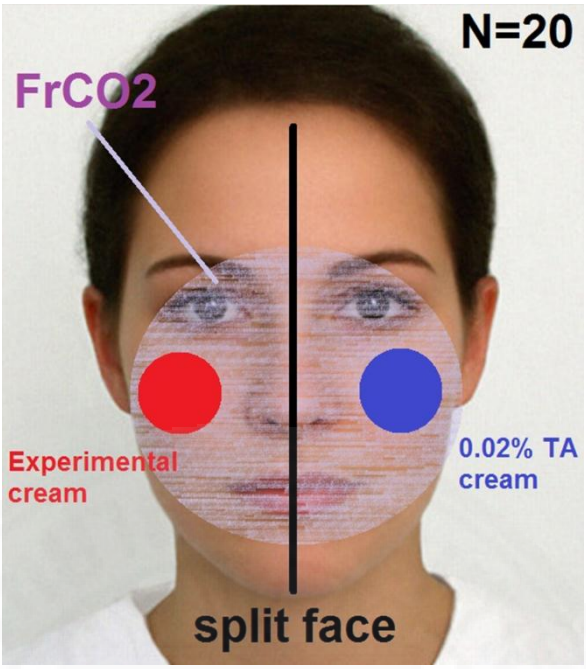


Figure 3.4 Methodology

3.9 Outcome measurement

All subjects were evaluated on the experimental day (day 1) (before and immediately after laser irradiation) and additional 6 follow-up visits including day 3, day 5, day 7, day 14, day 30, and day 60 after irradiation. The evaluation included questionnaires, facial examination, downtime and side effects reported by subjects, high resolution camera imaging, and facial scanning by the Antera device. The pain related to laser procedure was also recorded as the 0-10 pain scoring system immediately after the laser irradiation.

The facial examination included overall facial skin, erythema, scaling, crusting, dyspigmentation, PIH, skin texture, pore, acne scar, and other side effects. The questionnaires were also completed for downtime and side effects observed by the subjects, subject demographic data, Dermatology Quality of Life Index, the assessment of sunscreen knowledge, and patient satisfaction. Meanwhile, the photographic images were obtained by using a digital camera (Canon PowerShot G1 X Mark II Digital Camera; Canon Marketing Co., Ltd, Thailand) with the same camera settings, lighting, and positioning on every visit. The positioning was comprised of 5 positions; frontal, 45 degree left-lateral and right-lateral, and 90

degree left-lateral and right-lateral. Moreover, we used the expert panel assessment of photography by 3 blinded dermatologists to evaluate the subject's clinical from their picture. Meanwhile, the Antera facial scanning was obtained in a bid to evaluate the following parameters; hemoglobin (erythema), elevations (crusting and scaling), melanin, atrophic scars, and skin texture.

Figure 3.5 The Antera 3D facial scan device (40)

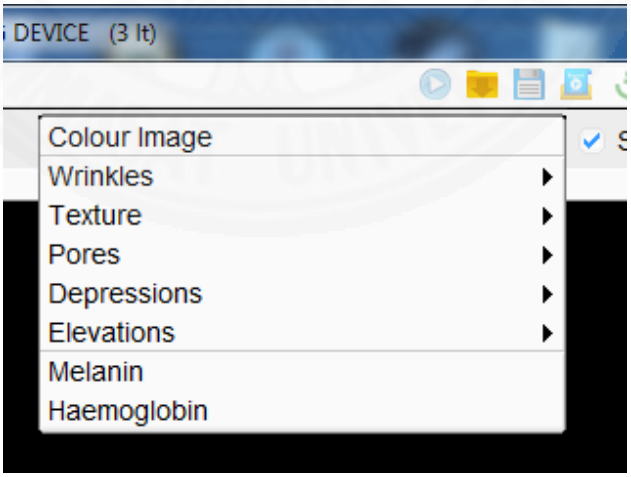


Figure 3.6 The parameter provided in the Antera 3D program (40)

Table 3.1 The schedule for the result evaluation

		Day 1 Before (base line)	Day 1 After	Day 3	Day 5	Day 7	Day 14	Day 30	Day 60
Clinical evaluation	Camera imaging								
	Expert panel								
Objective evaluation	Antera 3D								
Subjective evaluation	Demo graphic data								
	Down Time & S/E by subject								
	Other Ques.								
	Pain score								

3.10 Data collection

The data were corrected in the paper document, text file, and imaging file in the computer in every visit of the follow up. The case record form was used in this study to collect all the patient demographic data.

3.11 Data analysis

The patient demographic data and other descriptive statistic were analyzed by using percentage, mean, and SD. The comparison of the data between the side treated with the experimental cream and the side treated with the 0.02% TA cream were analyzed by using independent t-test and Mann Whitney U test. Meanwhile, the comparison of the data among times and the comparison between days were analyzed

by using Friedman test, Post Hoc test, and Wilcoxon Signed Ranks test with the P-value adjusting by using Bonferroni method.

3.12 Ethical consideration

This research has been approved by the Human Research Ethics Committee of Thammasat University No.1 Faculty of Medicine (Number of COA: 056/2017, Project number: MTU-EC-OO-2-119/59).

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Patient demographic data

Twenty subjects (12 males, 8 females) with the mean±SD age of 37.55±9.41 years were enrolled and completed the study. In details, most of them were skin phototype IV (11 subjects; 55%). In addition, 6 subjects (30%) were skin phototype III and 2 subjects (10%) were skin phototype V. Moreover, all subjects had no serious underlying disease except of hyperthyroid (1 subject; 5%), allergic rhinitis (1 subject; 5%), and gastritis (2 subjects; 10%), which all were in controlled. For the facial problem, most subjects had acne (10 subjects; 50%), oily face (9 subjects; 45%), freckle (4 subjects; 20%), melasma (2 subjects; 10%), and dry face (2 subjects; 10%) respectively. For the history of laser taken, 14 subjects (70%) had taken facial laser irradiation before (2 subjects; 10% had taken $FrCO_2$) with the last session held up before 3 months ago. Finally, 2 subjects (10%) had taken botox and filler injection on their face with the last session held up before 3 months ago.

Table 4.1 Patient demographic data

Variable	N	%
Sex		
Male	12	60.00
Female	8	40.00
Age	37.55±9.41/ 37.50	
Fitzpatrick skin type		
1	0	0.00
2	0	0.00
3	6	30.00
4	11	55.00
5	2	10.00
6	0	0.00
Underlying disease		
No	18	90.00
Yes	2	10.00
Hyperthyroid	1	5.00
Allergic rhinitis	1	5.00
Gastritis	2	10.00

Variable	N	%
Facial skin problem		
No	8	40.00
Yes	12	60.00
Acne	10	50.00
Melasma	2	10.00
Freckle	4	20.00
Oily face	9	45.00
Dry face	2	10.00
Previous treatment in the past		
Topical drug (before 3 months ago)	9	45.00
Oral drug (before 6 months ago)	6	30.00
Laser (before 3 months ago)	14	70.00
History of medical allergy		
No	16	80.00
Yes	4	20.00
History of skin hydration loosing		
> 10 min showering	8	40.00
> 2 times/day taking a bath	5	25.00
Taking a bath with warm or hot water	7	35.00
> 6 hrs/day living in the air conditioning room	14	70.00
History of facial cleansing product using		
Soap (solid)	5	25.00
Liquid gel	7	35.00
Cream or foam	7	35.00
Tap water	1	5.00
History of facial toner using		
Never	14	70.00
Yes, now using	3	15.00
Used to	3	15.00
History of topical vit.A derivative product using		
Never	13	65.00
Yes, now using	0	0.00
Used to (before 3 months ago)	7	35.00
History of topical acne treatment product using		
Never	15	75.00
Yes, now using	0	0.00
Used to (before 3 months ago)	5	25.00
History of facial treatment in the past		
No	11	55.00
Yes (before 3 months ago)	9	45.00
AHA	8	40.00
Ionto	4	20.00
Phono	2	10.00
Microdermabrasion	5	25.00

Variable	N	%
History of laser taking in the past		
No	8	40.00
Yes (before 3 months ago)	12	60.00
IPL	2	10.00
CO_2	5	25.00
Qs Nd:Yag	2	10.00
Long pulse	0	0.00
Radiofrequency (RF)	1	5.00
Fractional laser	2	10.00
History of filler injection in the past		
No	18	90.00
Yes (before 3 months ago)	2	10.00
History of botox injection in the past		
No	18	90.00
Yes (before 3 months ago)	2	10.00
History of oral vit.A derivative drug taking		
Never	15	75.00
Yes, now taking	0	0.00
Used to (before 6 months ago)	5	25.00

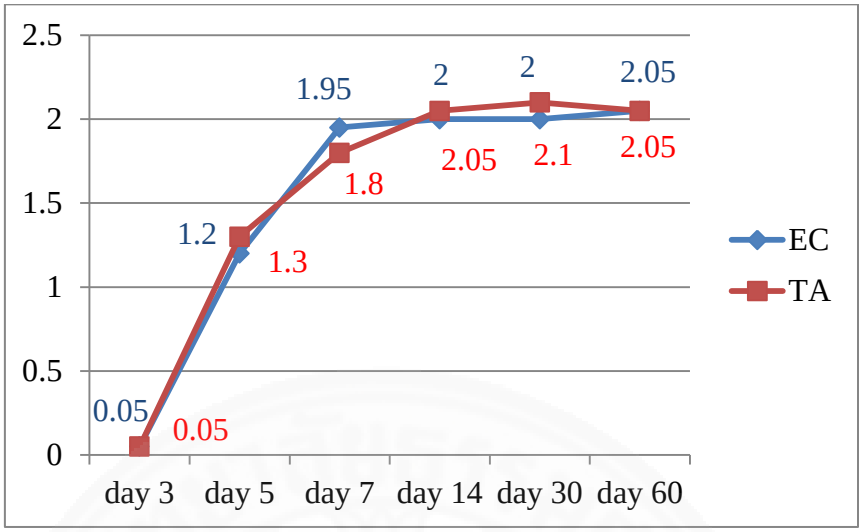
4.2 The expert panel assessment of photography

We evaluated the clinical of the subjects by using the expert panel assessment of the photography. In details, all pictures of the subjects' face from day 1 to day 60 post irradiation were evaluated and scored by 3 blinded dermatologists. The assessment was divided into three categories; the downtime, side effect, and the laser treatment result.

4.2.1 The downtime

For the downtime, the expert panel assessment revealed that swelling were averagely rated as not change at day 3, mild improve at day 5 to day 7, and moderate improve at day 14 to day 60 in both the experimental cream treated side and the 0.02% TA cream treated side. In the same way, redness was not changes at day3, mild improve at day 5 to day 7, and moderate improve at day 14 to day 60. On the other hand, scaling and crusting were not change until day 5, but then, were moderate improve from day 7 to day 60 in both sides of the face. There was no significant difference of the improved downtime between both regimens (p-value > 0.05).

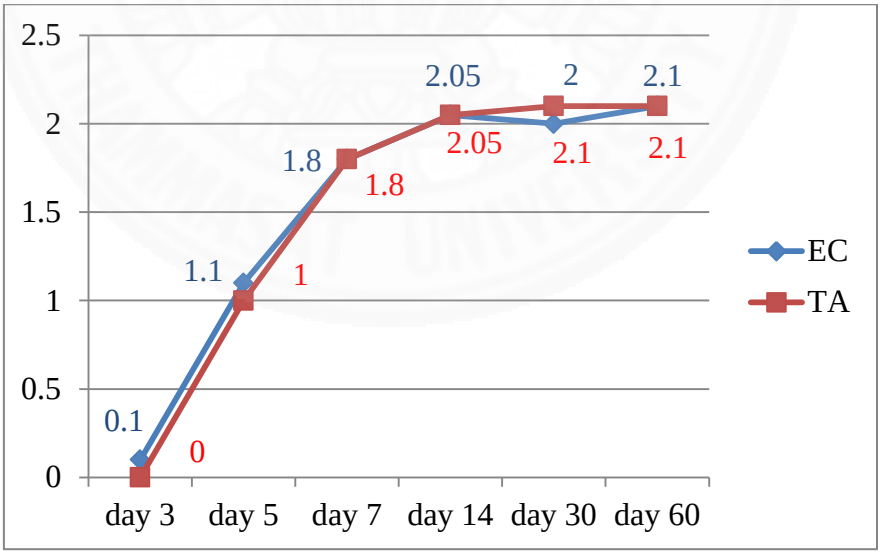
Table 4.2 The expert panel assessment of the downtime; swelling



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

This data was the changes of the swelling compared with those in day 1 immediately after irradiation (0 = no change, 1 = mild improve, 2 = moderate improve, 3 = a lot improve, 4 = very improve)

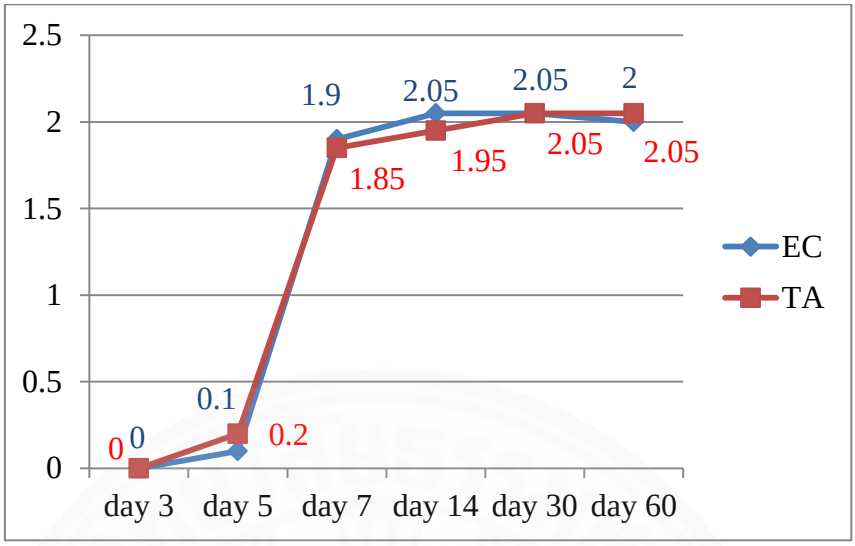
Table 4.3 The expert panel assessment of the downtime; redness



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

This data was the changes of the redness compared with those in day 1 immediately after irradiation (0 = no change, 1 = mild improve, 2 = moderate improve, 3 = a lot improve, 4 = very improve)

Table 4.4 The expert panel assessment of the downtime; crusting and scaling



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

This data was the changes of the crusting and scaling compared with those in day 1 immediately after irradiation (0 = no change, 1 = mild improve, 2 = moderate improve, 3 = a lot improve, 4 = very improve)

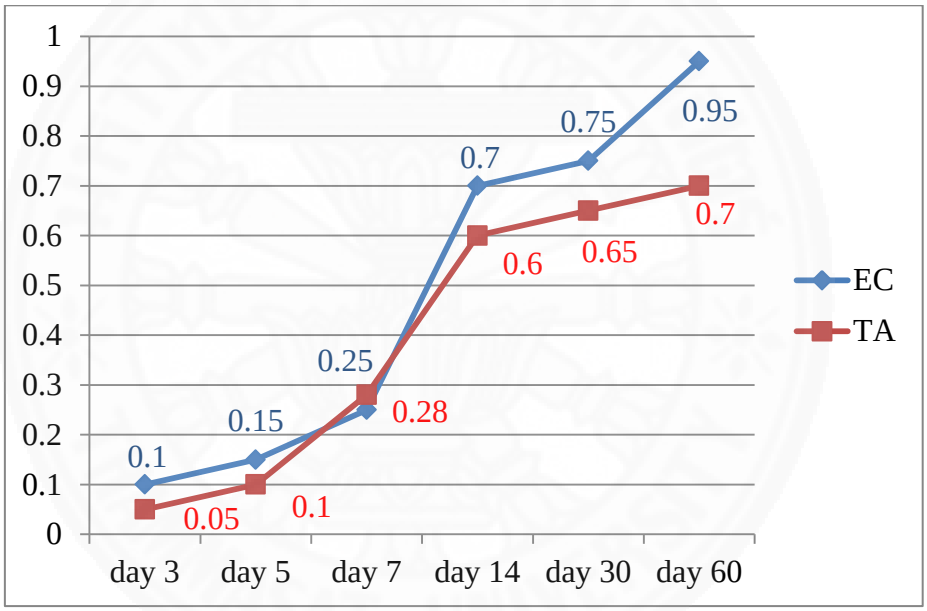
Variables	Day 3			Day 5			Day 7			Day 14			Day 30			Day 60		
	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value
Downtime																		
Swelling	0.05±0.22	0.05±0.22	1.000	1.20±0.52	1.30±0.57	0.539	1.95±0.22	1.80±0.52	0.211	2.00±0.00	2.05±0.22	0.317	2.00±0.00	2.10±0.31	0.152	2.05±0.22	2.05±0.22	1.000
No change	19 (95.0)	19 (95.0)		1 (5.0)	1 (5.0)		1 (5.0)	5 (25.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mild improve	1 (5.0)	1 (5.0)		14 (70.0)	12 (60.0)		19 (95.0)	14 (70.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate improve	0 (0.0)	0 (0.0)		5 (25.0)	7 (35.0)		0 (0.0)	1 (5.0)		20 (100.00)	19 (95.0)		20 (100.0)	18 (90.0)		19 (95.0)	19 (95.0)	
A lot improve	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	1 (5.0)		0 (0.0)	2 (10.0)		1 (5.0)	1 (5.0)	
Very improve	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Redness	0.10±0.31	0.00±0.00	0.152	1.10±0.55	1.00±0.56	0.568	1.80±0.41	1.80±0.52	0.943	2.05±0.22	2.05±0.22	1.000	2.00±0.00	2.10±0.31	0.152	2.10±0.31	2.10±0.31	1.000
No change	18 (90.0)	20 (100.0)		2 (10.0)	3 (15.0)		4 (20.0)	5 (25.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mild improve	2 (10.0)	0 (0.0)		14 (70.0)	14 (70.0)		16 (80.0)	14 (70.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate improve	0 (0.0)	0 (0.0)		4 (20.0)	3 (15.0)		0 (0.0)	0 (0.0)		19 (95.0)	19 (95.0)		20 (100.0)	18 (90.0)		18 (90.0)	18 (90.0)	
A lot improve	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (5.0)	1 (5.0)		0 (0.0)	2 (10.0)		2 (10.0)	2 (10.0)	
Very improve	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Crusting and scaling	0.00±0.00	0.00±0.00	1.000	0.10±0.01	0.20±0.05	0.493	1.90±0.31	1.85±0.49	0.959	2.05±0.22	1.95±0.22	0.163	2.05±0.22	2.05±0.22	1.000	2.00±0.00	2.05±0.22	0.317
No change	20 (100.0)	20 (100.0)		18 (90.0)	17 (85.0)		0 (0.0)	1 (5.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mild improve	0 (0.0)	0 (0.0)		2 (10.0)	2 (10.0)		2 (10.0)	1 (5.0)		0 (0.0)	1 (5.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate improve	0 (0.0)	0 (0.0)		0 (0.0)	1 (5.0)		18 (90.0)	18 (90.0)		19 (95.0)	19 (95.0)		19 (95.0)	19 (95.0)		20 (100.0)	19 (95.0)	
A lot improve	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (5.0)	0 (0.0)		1 (5.0)	1 (5.0)		0 (0.0)	1 (5.0)	
Very improve	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Table 4.5 The expert panel assessment of the photography; downtime
EC = experimental cream, TA = 0.02% TA cream
This data was the changes of the downtime compared with those in day 1 immediately after irradiation
(0 = no change, 1 = mild improve, 2 = moderate improve, 3 = a lot improve, 4 = very improve)
(Mann-Whitney U Test)

4.2.2 Side effect

For the side effect, the expert panel assessment showed that PIH were not seen in the first 4 visits (day 1 to day 7). After that, they were observed at day 14 until the end of the study. For the intensity, they were averagely rated as minimal PIH from day 14 to day 60 in both the experimental cream treated side and the 0.02% TA cream treated side. Moreover, acneiform eruption was averagely rated as not seen from day 1 to day 60 in both sides of the face. There was no significant difference of the side effects between both regimens (p-value > 0.05).

Table 4.6 The expert panel assessment of the PIH



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

This data was the changes of PIH compared with those in day 1 immediately after irradiation (0 = no change, 1 = minimal PIH, 2 = mild PIH, 3 = moderate PIH, 4 = severe PIH)

Variables	Day 3			Day 5			Day 7			Day 14			Day 30			Day 60		
	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value
S/E																		
PIH	-0.10±0.01	0.05±0.05	0.652	-0.15±0.10	-0.10±0.10	0.862	-0.25±0.20	-0.20±0.20	0.877	-0.70±0.60	0.60±0.62	0.431	-0.75±0.77	-0.65±0.66	0.666	-0.95±0.91	-0.70±0.81	0.349
No change	18 (90.0)	19 (95.0)		17 (85.0)	18 (90.0)		15 (75.0)	16 (80.0)		9 (45.0)	9 (45.0)		9 (45.0)	9 (45.0)		8 (40.0)	9 (45.0)	
Minimal PIH	2 (10.0)	1 (5.0)		3 (15.0)	2 (10.0)		5 (25.0)	4 (20.0)		8 (40.0)	10 (50.0)		7 (35.0)	10 (50.0)		6 (30.0)	9 (45.0)	
Mild PIH	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		3 (15.0)	1 (5.0)		4 (20.0)	0 (0.0)		5 (25.0)	1 (5.0)	
Moderate PIH	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	1 (5.0)		1 (5.0)	1 (5.0)	
Severe PIH	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Acneiform eruption	-0.05±0.22	0.05±0.22	1.000	-0.05±0.22	-0.05±0.22	1.000	-0.15±0.49	-0.10±0.31	0.959	-0.10±0.45	0.20±0.52	0.323	-0.10±0.31	-0.15±0.37	0.637	-0.05±0.22	-0.10±0.31	0.553
No change	19 (95.0)	19 (95.0)		19 (95.0)	19 (95.0)		18 (90.0)	18 (90.0)		19 (95.0)	17 (85.0)		18 (90.0)	17 (85.0)		19 (95.0)	18 (90.0)	
Minimal eruption	1 (5.0)	1 (5.0)		1 (5.0)	1 (5.0)		1 (5.0)	2 (10.0)		0 (0.0)	2 (10.0)		2 (10.0)	3 (15.0)		1 (5.0)	2 (10.0)	
Mild eruption	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (5.0)	0 (0.0)		1 (5.0)	1 (5.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate eruption	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Severe eruption	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

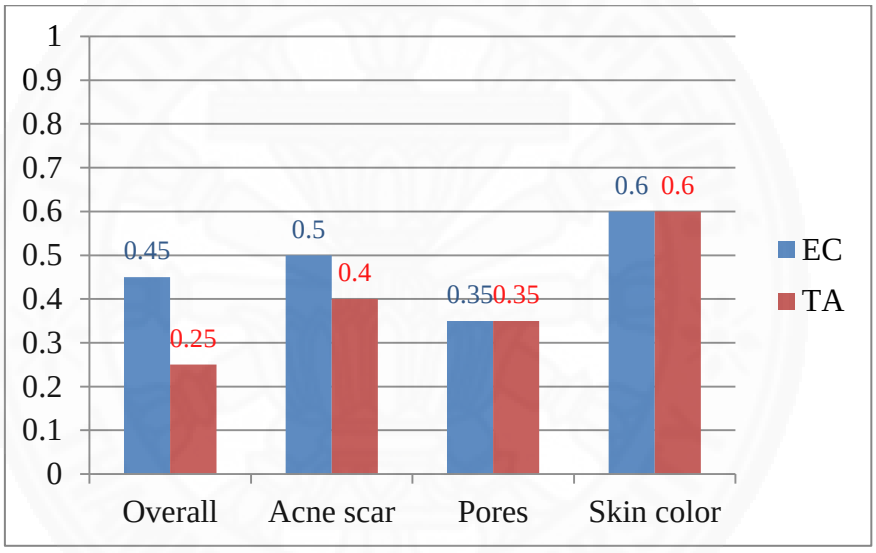
Table 4.7 The expert panel assessment of the photography; side effect
EC = experimental cream, TA = 0.02% TA cream
This data was the changes of side effects compared with those in day 1 immediately after irradiation

(Mann-Whitney U Test)

4.2.3 The laser treatment result

For the expert panel assessment of the laser treatment result, the average score for the overall result were rated as “not change” in both day 30 and day 60 post irradiation, and in both the experimental cream treated side and the 0.02% TA cream treated side with no difference (p-value > 0.05). In details, all parameters including acne scar, pores, and skin color were averagely rated as “not change” in both the experimental cream treated side and the 0.02% TA cream treated side, and in both day 30 and day 60 with no significant difference (p-value > 0.05).

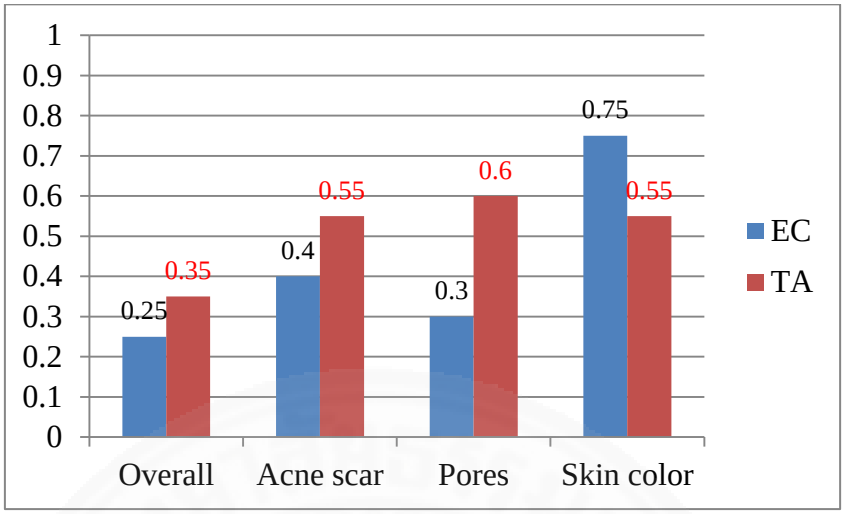
Table 4.8 The expert panel assessment of the laser treatment result in day 30



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

This data was the laser treatment result compared with those before irradiation (0 = no change, 1 = mild improve, 2 = moderate improve, 3 = a lot improve, 4 = very improve, -1 = mild worse, -2 = moderate worse, -3 = a lot worse, -4 = very worse)

Table 4.9 The expert panel assessment of the laser treatment result in day 60



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

This data was the laser treatment result compared with those before irradiation (0 = no change, 1 = mild improve, 2 = moderate improve, 3 = a lot improve, 4 = very improve, -1 = mild worse, -2 = moderate worse, -3 = a lot worse, -4 = very worse)

Table 4.10 The expert panel assessment of photography; the laser treatment result

	Day 30			**Day 60**		
	EC	**TA**	**P-value**	**EC**	**TA**	**P-value**
Acne scar	0.50±0.61	0.40±0.75	0.784	0.40±0.60	0.55±0.69	0.320
Very worse (-4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
A lot worse (-3)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate worse (-2)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mild worse (-1)	1 (5.0)	3 (15.0)		1 (5.0)	2 (10.0)	
Not change (0)	8 (40.0)	6 (30.0)		10 (50.0)	5 (25.0)	
Mild improve (1)	11 (55.0)	11 (55.0)		9 (45.0)	13 (65.0)	
Moderate improve (2)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
A lot improve (3)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Very improve (4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Pores	0.35±0.67	0.35±0.75	0.917	0.30±0.66	0.60±0.69	0.100
Very worse (-4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
A lot worse (-3)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate worse (-2)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mild worse (-1)	2 (10.0)	3 (15.0)		2 (10.0)	2 (10.0)	
Not change (0)	9 (45.0)	7 (35.0)		10 (50.0)	4 (20.0)	
Mild improve (1)	9 (45.0)	10 (50.0)		8 (40.0)	14 (70.0)	
Moderate improve (2)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
A lot improve (3)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Very improve (4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Skin color	0.60±0.68	0.60±0.75	0.949	0.75±0.79	0.55±0.83	0.274
Very worse (-4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

	Day 30			Day 60		
	EC	**TA**	**P-value**	**EC**	**TA**	**P-value**
A lot worse (-3)	0 (0.0)	0 (0.0)		1 (5.0)	1 (5.0)	
Moderate worse (-2)	0 (0.0)	1 (5.0)		0 (0.0)	0 (0.0)	
Mild worse (-1)	14 (70.0)	12 (60.0)		13 (65.0)	9 (45.0)	
Not change (0)	4 (20.0)	5 (25.0)		5 (25.0)	9 (45.0)	
Mild improve (1)	2 (10.0)	2 (10.0)		1 (5.0)	1 (5.0)	
Moderate improve (2)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
A lot improve (3)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Very improve (4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Overall result	0.45±0.60	0.25±0.72	0.386	0.25±0.64	0.35±0.67	0.589
Very worse (-4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
A lot worse (-3)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Moderate worse (-2)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Mild worse (-1)	1 (5.0)	3 (15.0)		2 (10.0)	2 (10.0)	
Not change (0)	9 (45.0)	9 (45.0)		11 (55.0)	9 (45.0)	
Mild improve (1)	10 (50.0)	8 (40.0)		7 (35.0)	9 (45.0)	
Moderate improve (2)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
A lot improve (3)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Very improve (4)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

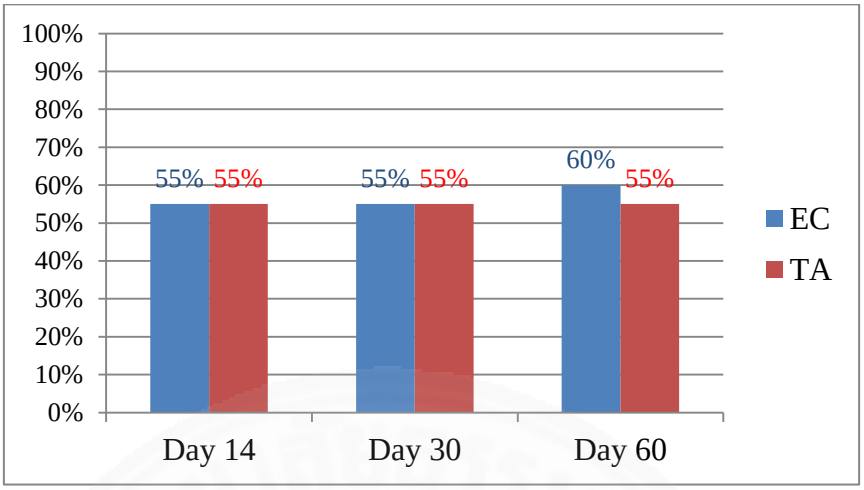
Mann-Whitney U test

EC = experimental cream, TA = 0.02% TA cream

4.2.4 The incidence of PIH

For PIH occurred in this study, they were started to be observed at day 14 until the end of the study. The average intensity of the PIH was minimal PIH in both the experimental cream treated side and the steroid treated side. At the end of the study (day 60), the incidence of PIH were 60% in the experimental cream treated side, and 55% in the steroid treated side. Moreover, there was no significant different in the incidence of PIH between both regimens (p-value > 0.05).

Table 4.11 The incidence of PIH at day 14, day 30, and day 60



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

Table 4.12 The incidence and the intensity of PIH at day 14, day 30, and day 60

	Day 14		**Day 30**		**Day 60**	
	EC	**TA**	**EC**	**TA**	**EC**	**TA**
No PIH	9(45%)	9(45%)	9(45%)	9(45%)	8(40%)	9(45%)
Minimal PIH	8(40%)	10(50%)	7(35%)	10(50%)	6(30%)	9(45%)
Mild PIH	3(15%)	1(5%)	4(20%)	0(0%)	5(25%)	1(5%)
Moderate PIH	0(0%)	0(0%)	0(0%)	1(5%)	1(5%)	1(5%)
Severe PIH	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
Total PIH	11(55%)	11(55%)	11(55%)	11(55%)	12(60%)	11(55%)

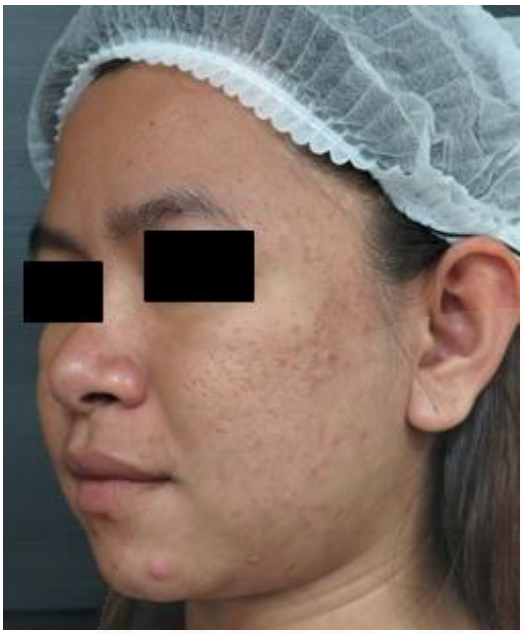
EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

4.3 The pictures of the patient's face

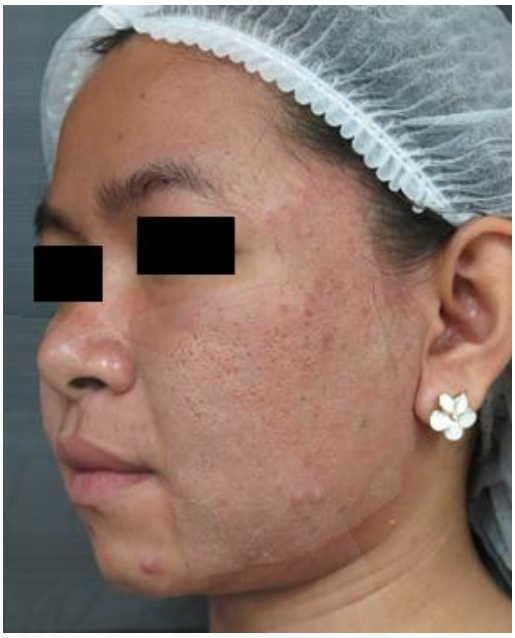
The photographic images were obtained by using a high resolution digital camera with the same camera settings, lighting, and positioning on every visit. The pictures below are 2 examples from 20 of them.

4.3.1 Subject number 1

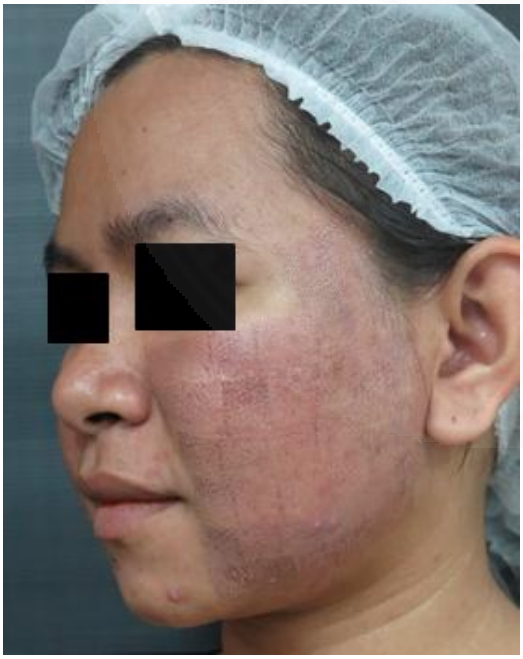
4.3.1.1 The side treated with the experimental cream



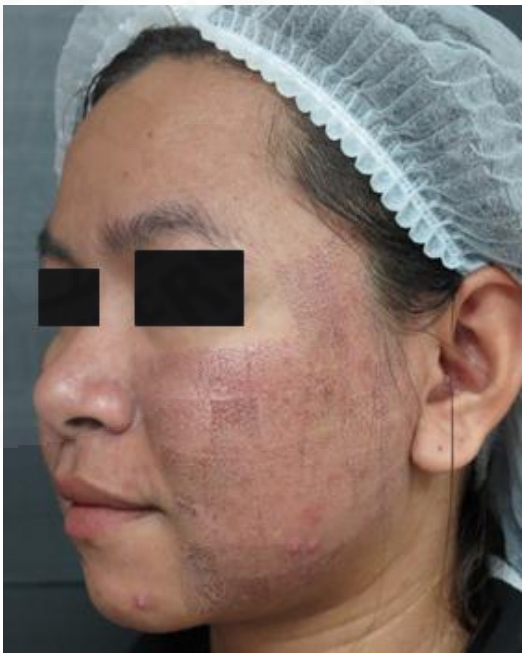
Day 1 (before irridiation)



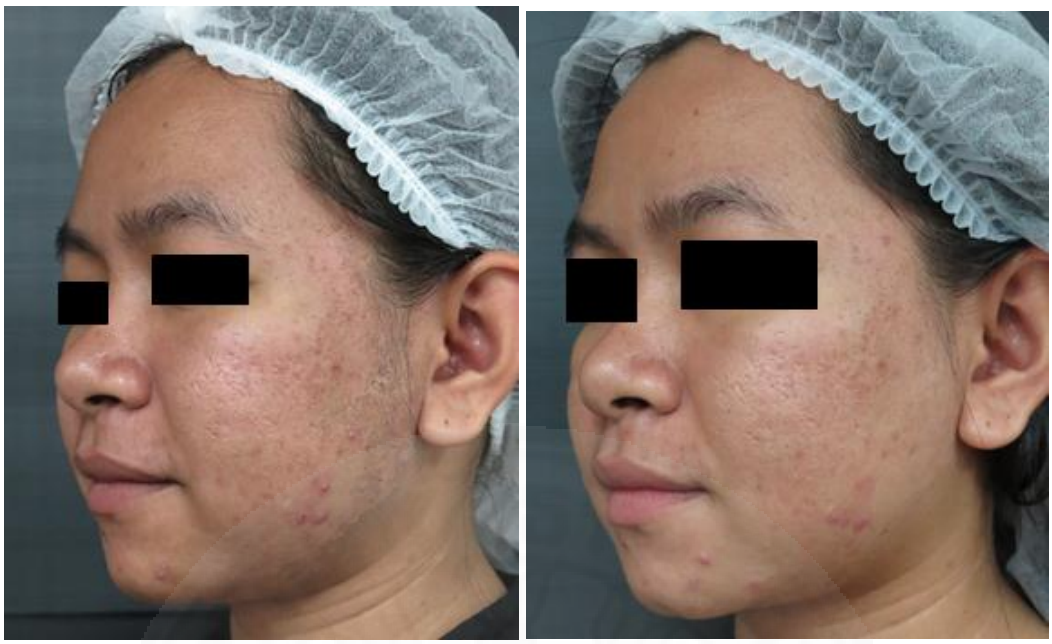
Day 1 (immediately after irridiation)



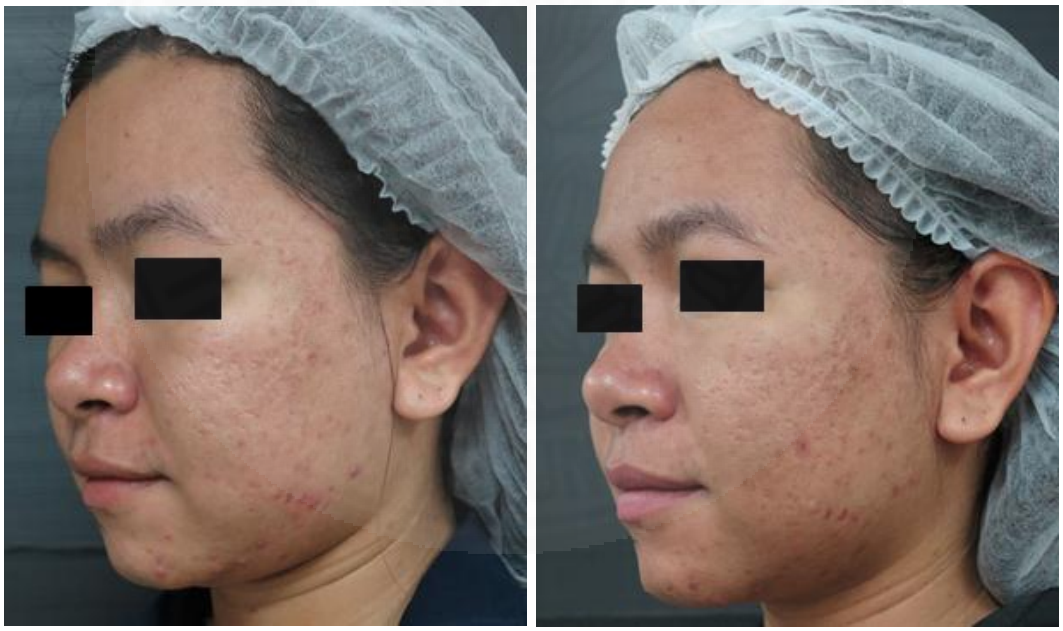
Day 3



Day 5



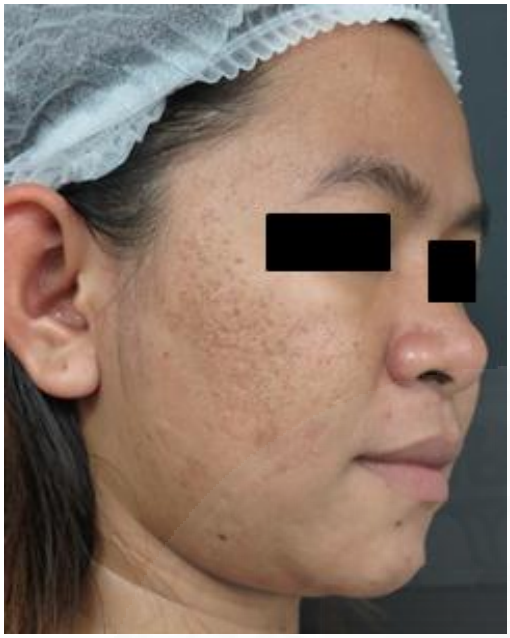
Day 7 Day 14



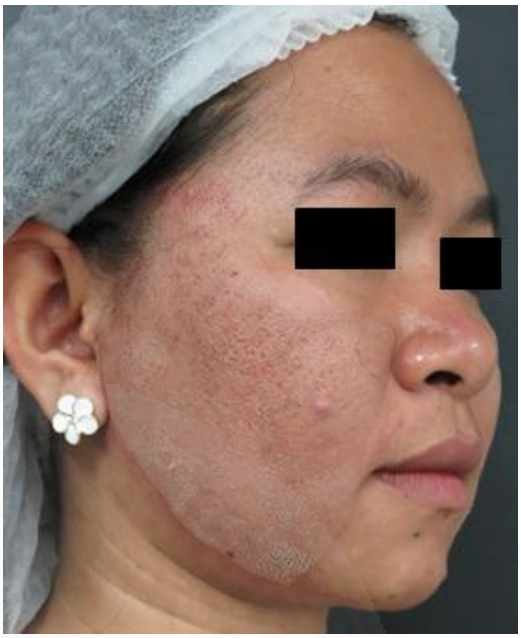
Day 30 Day 60

Figure 4.1 The pictures of the side treated with the experimental cream in subject number 1 at day 1 to day 60

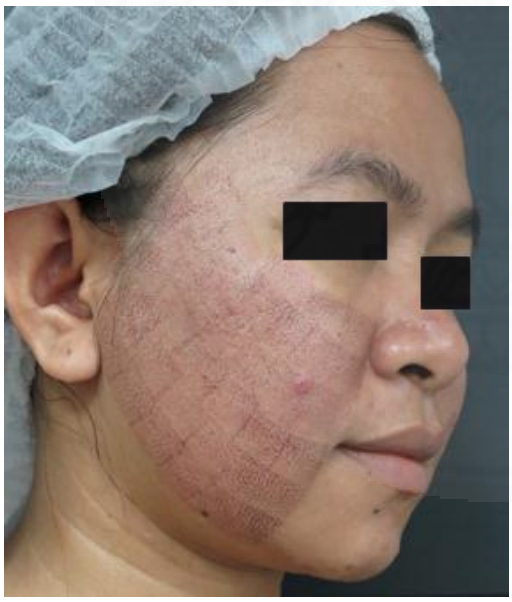
4.3.1.2 The side treated with the 0.02% TA cream



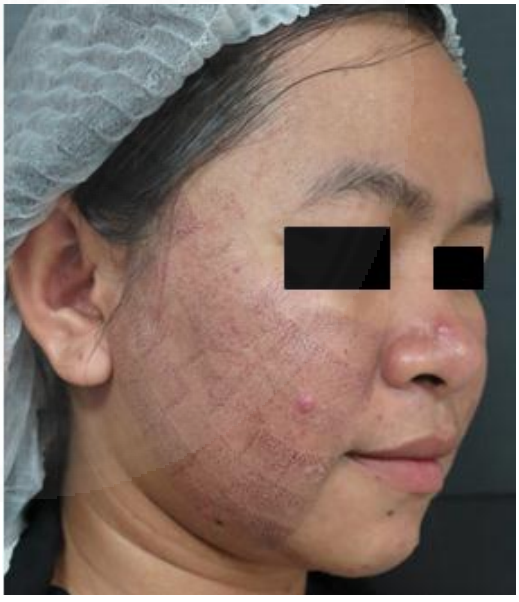
Day 1 (before irridiation)



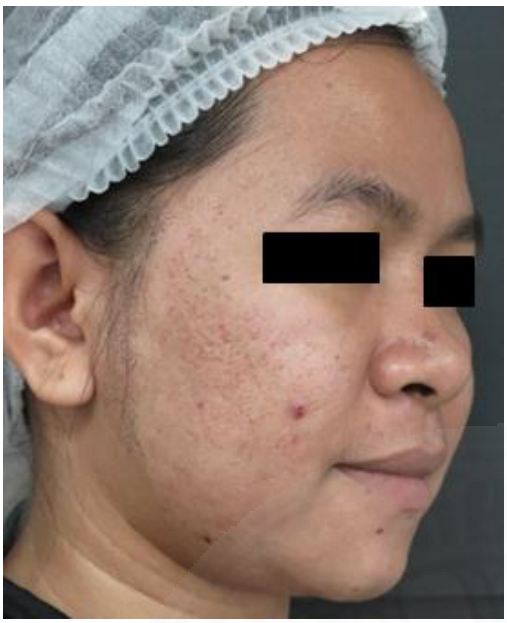
Day 1 (immediately after irridiation)



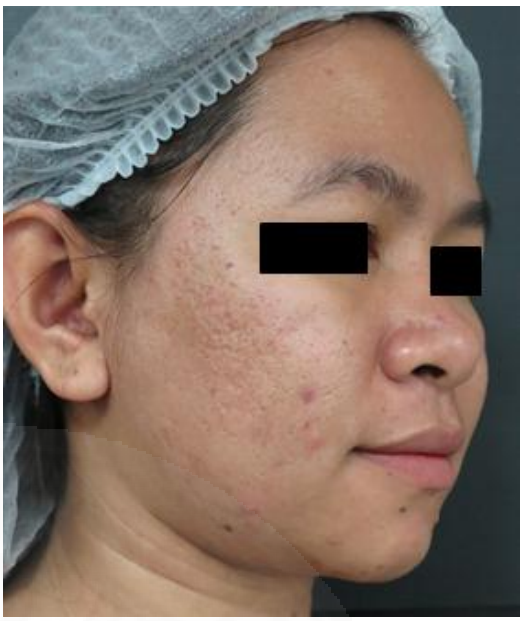
Day 3



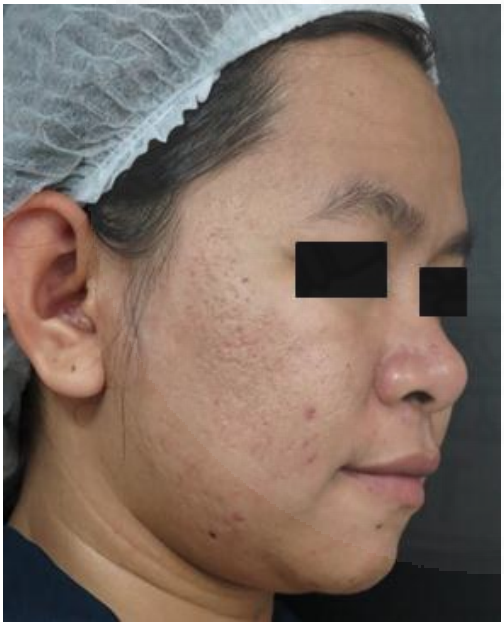
Day 5



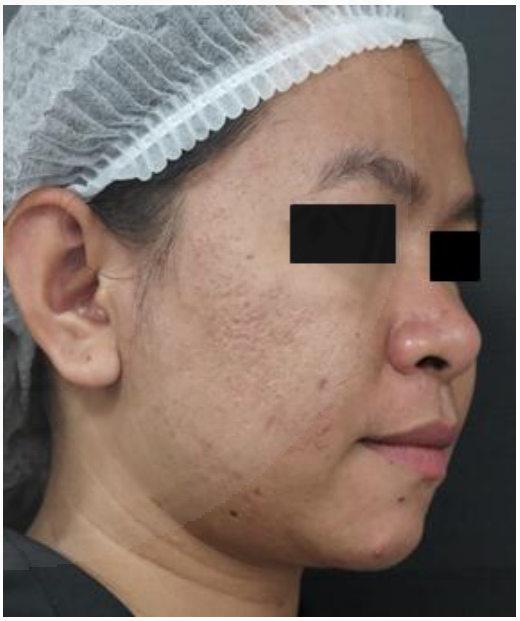
Day 7



Day 14



Day 30

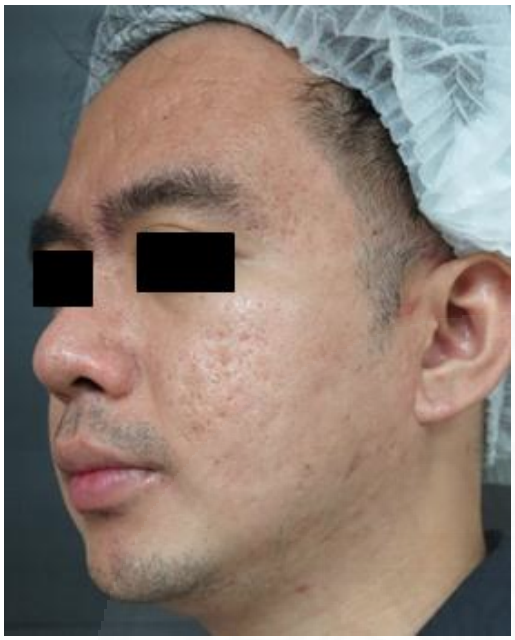


Day 60

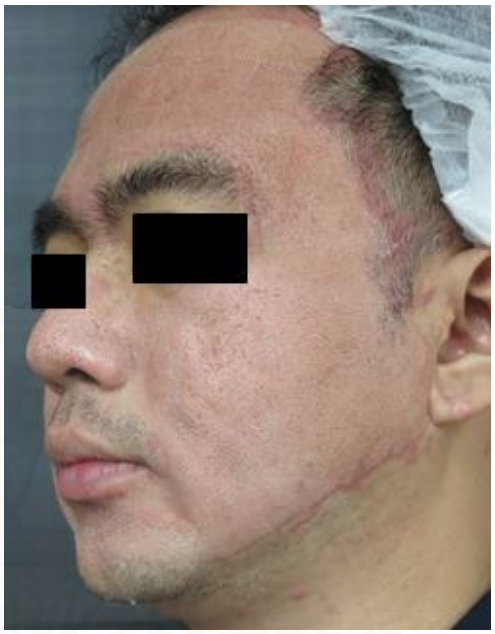
Figure 4.2 The pictures of the side treated with the 0.02% TA cream in subject number 1 at day 1 to day 60

4.3.2 Subject number 2

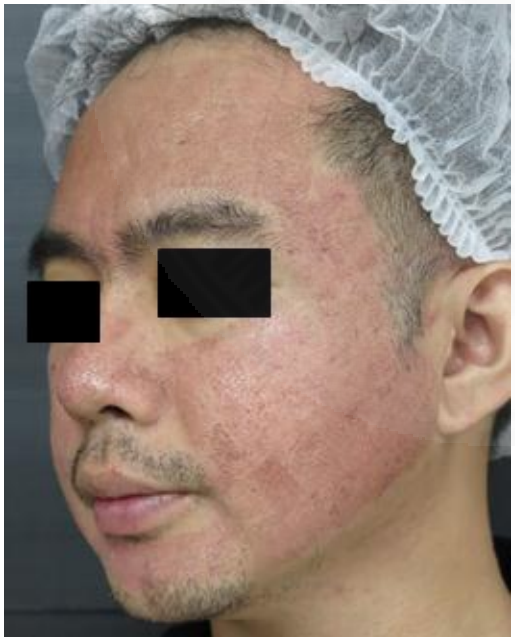
4.3.2.1 The side treated with the experimental cream



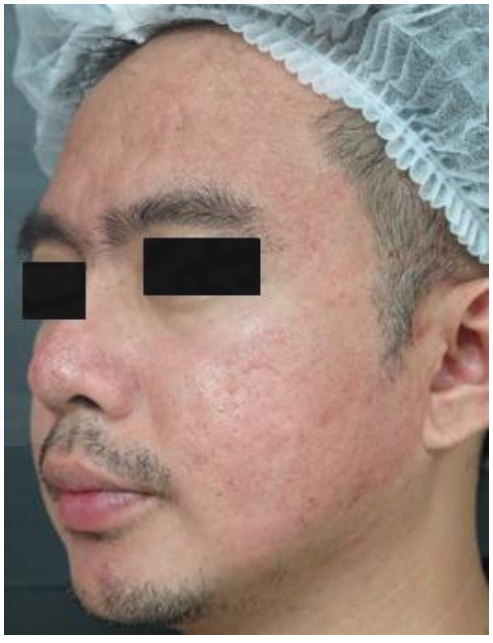
Day 1 (before irridiation)



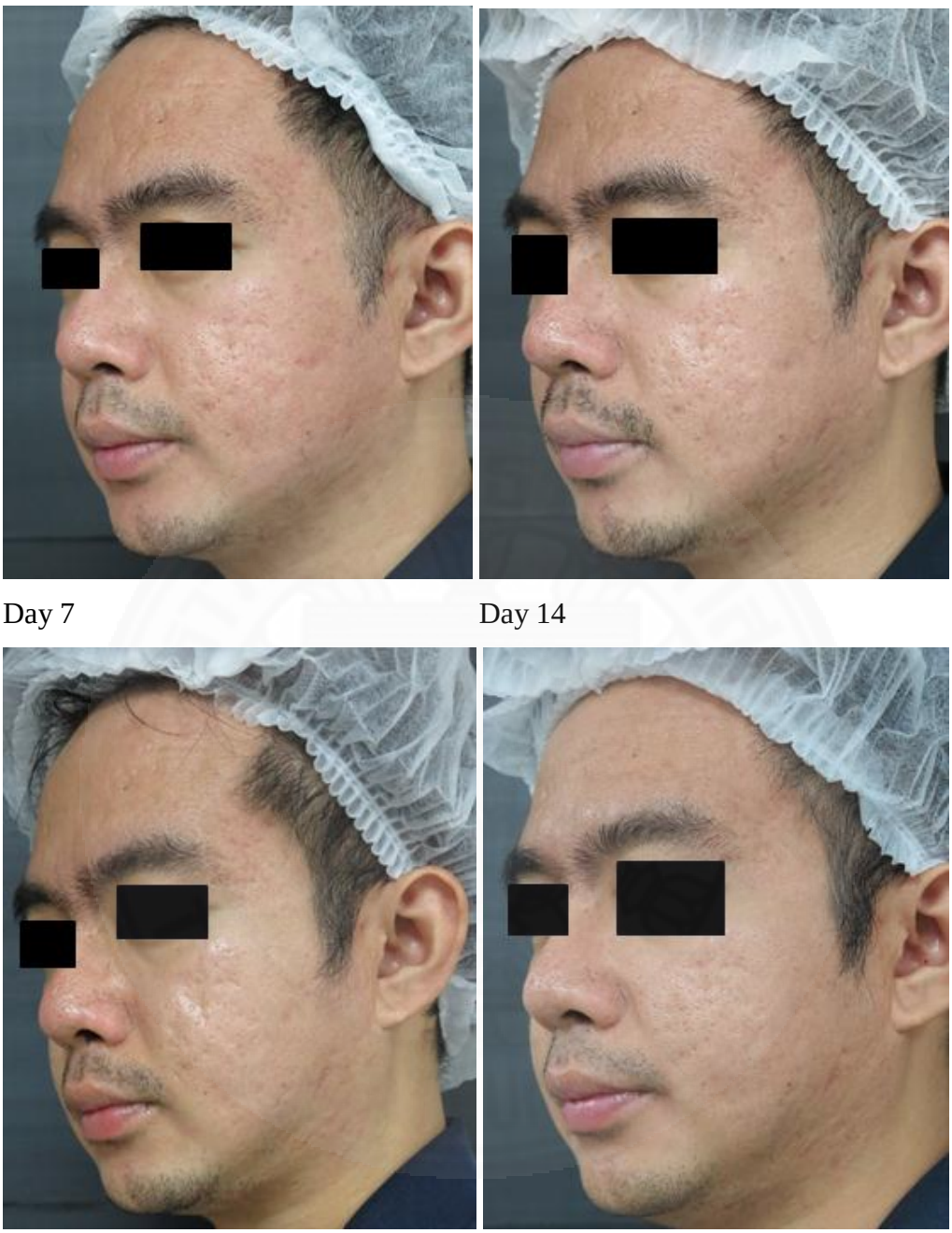
Day 1 (immediately after irridiation)



Day 3



Day 5

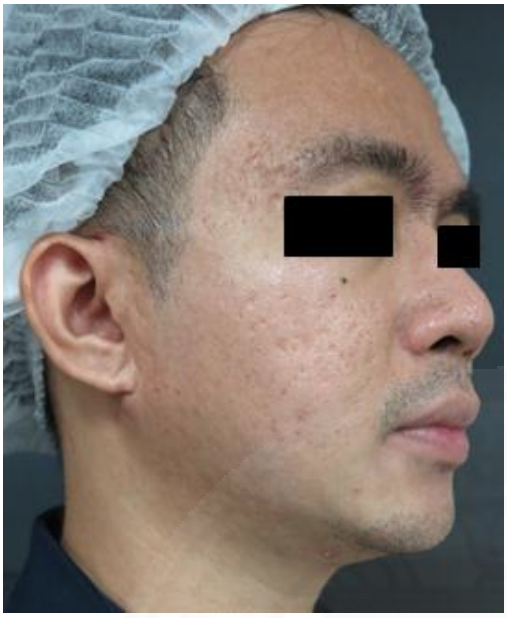


Day 7 Day 14

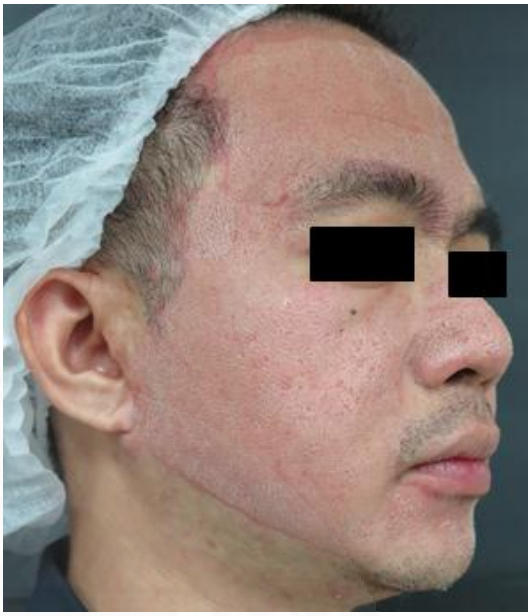
Day 30 Day 60

Figure 4.3 The pictures of the side treated with the experimental cream in subject number 2 at day 1 to day 60

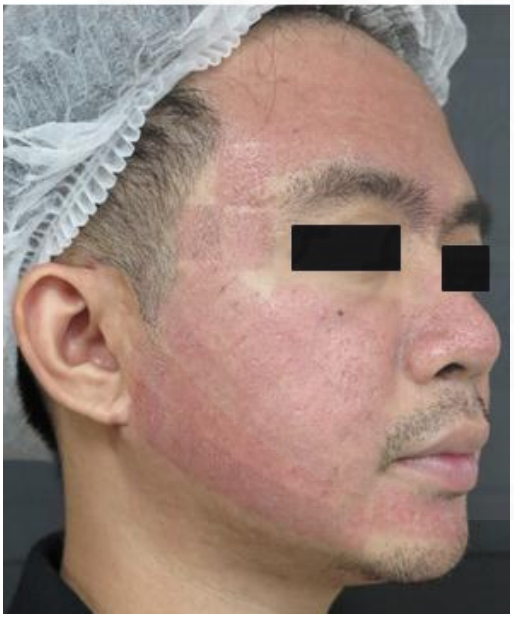
4.3.2.2 The side treated with the 0.02% TA cream



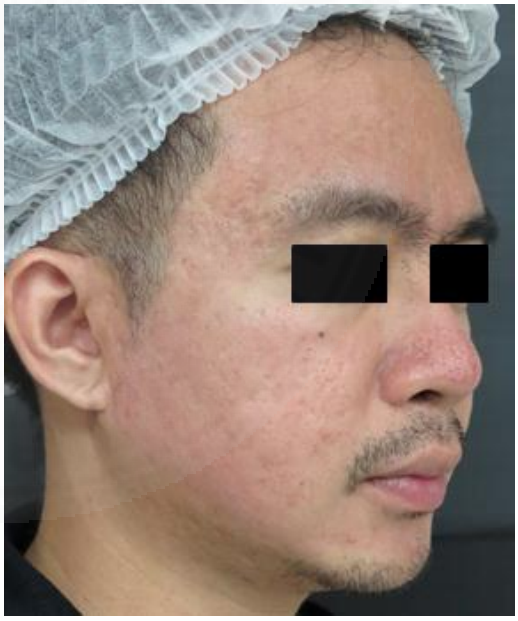
Day 1 (before irridiation)



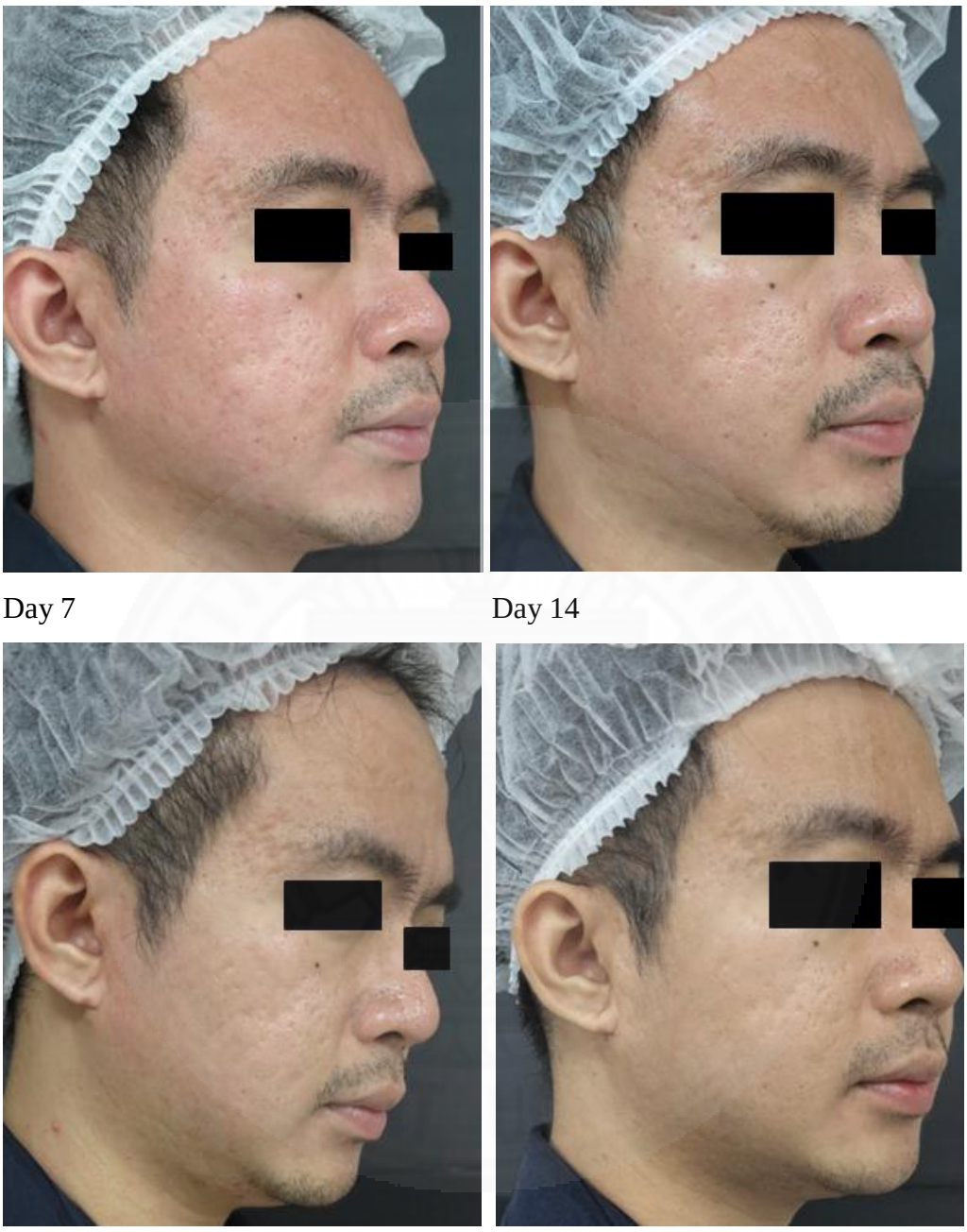
Day 1 (immediately after irridiation)



Day 3



Day 5



Day 7 Day 14

Day 30 Day 60

Figure 4.4 The pictures of the side treated with the 0.02% TA cream in subject number 2 at day 1 to day 60

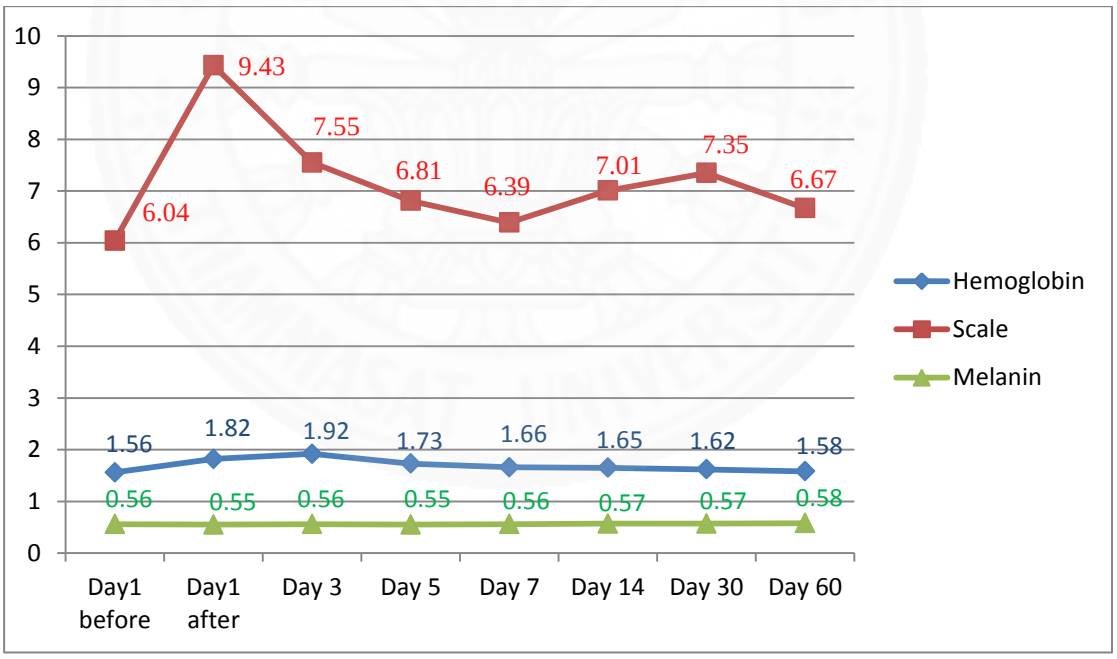
4.4 The biometric facial scan (Antera 3D)

In every visits, the Antera 3D facial scanning was obtained in a bid to evaluate the following parameters; hemoglobin (erythema), elevations (scaling), melanin, depressions (atrophic scars), and skin texture.

4.4.1 The side treated with the experimental cream

In the experimental cream treated side, hemoglobin obviously rose up to the peak (1.92) at day 3 postoperatively and then significantly decreased to 1.58 at day 60. Scale undoubtedly reached the peak (9.43) immediately after the laser irradiation and declined significantly to 6.67 at day 60. Besides, other parameters including melanin had no significant change during the study period.

Table 4.13 The changes of hemoglobin, scale, and melanin in the experimental cream treated side evaluated by the Antera 3D device



	Before	After	Day 3	Day 5	Day 7
Atrophic scar	11.44±7.90	12.48±9.03	10.57±7.68	11.81±9.17	12.21±9.84
Hemoglobin	1.56±0.17[1*,2*,3*,4*,5*]	1.82±0.13[1*,6*,7*,8*,9*,10*,11*]	1.92±0.17[2*,6*,12*,13*,14*,15*,16*]	1.73±0.16[3*,7*,12*,17*,18*,19*,20*]	1.66±0.16[4*,8*,13*,17*,21*]
Melanin	0.56±0.07[1*,2*,3*]	0.55±0.05[4*,5*,6*,7*]	0.56±0.06[4*,8*,9*]	0.55±0.06[5*,10*,11*,12*]	0.56±0.05[9*,13*,14*,15*]
scale	6.04±3.57[1*]	9.43±5.14[1*,2*,3*,6*,7*]	7.55±4.13	6.81±4.78[4*]	6.39±4.11[5*]
Texture	26.08±10.62	28.42±12.40	25.52±10.19	26.81±12.30	27.30±13.30
	Day 14	**Day 30**	**Day 60**	**P-value**	
Atrophic scar	12.27±8.62	13.19±8.93	12.26±8.98	0.062[2]	
Hemoglobin	1.65±0.14[3*,9*,14*,18*,22*]	1.62±0.15[10*,15*,19*]	1.58±0.17[11*,16*,20*,21*,22*]	**<0.001[1]**	
Melanin	0.57±0.07[1*,5*,10*,15*]	0.57±0.07[2*,6*,11*,14*]	0.58±0.06[3*,7*,12*,15*]	**0.008[1]**	
scale	7.01±4.39[4*]	7.35±4.08	6.67±4.16[5*]	**<0.001[2]**	
Texture	27.29±11.61	28.48±12.08	27.39±12.16	0.168[2]	

Repeated Measure Analysis, Post Hoc: LSD

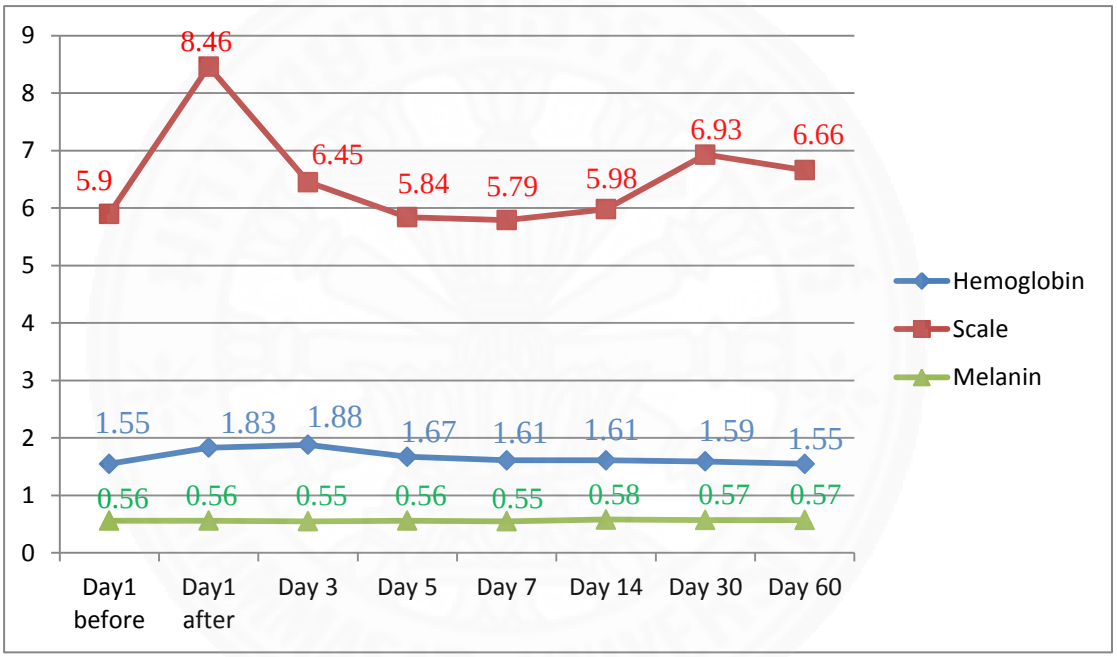
Friedman Test, Post Hoc: Wilcoxon Signed Ranks Test (P-value<0.002)

Table4.14 The biometric facial scan (Antera 3D) result of the side treated with the experimental cream

4.4.2 The side treated with the 0.02% TA cream

In the 0.02% TA cream treated side, hemoglobin also reached the peak (1.88) at day 3 and then significantly declined to the lowest point (1.55) at day 60. Scale rose up to the highest point (8.46) immediately after the laser irradiation and dropped significantly to 6.66 at day 60. Finally, other parameters including melanin had no significant change during the study period.

Table 4.15 The changes of hemoglobin, scale, and melanin in the 0.02% TA cream treated side evaluated by the Antera 3D device



	Before	After	Day 3	Day 5	Day 7
Atrophic scar	11.48±8.10	11.26±8.61	9.50±6.65	10.62±7.53	10.93±7.89
Hemoglobin	1.55±0.13[1*,2*,3*,4*]	1.83±0.14[1*,5*,6*,7*,8*,9*]	1.88±0.17[2*,10*,11*,12*,13*,14*]	1.67±0.14[3*,5*,10*,15*,16*,17*,18*]	1.61±0.14[4*,6*,11*,15*,19*]
Melanin	0.56±0.07[1*,2*]	0.56±0.05[3*,4*]	0.55±0.05[1*,3*,5*,6*,7*,8*]	0.56±0.06[2*,9*]	0.55±0.06[2*,6*,10*,11*,12*]
scale	5.90±3.72[1*]	8.46±5.10[1*,2*,3*,4*,5*]	6.45±3.21	5.84±3.61[2*]	5.79±3.88[3*]
Texture	26.03±10.85	26.70±11.83	23.84±8.80	24.86±10.18	25.25±10.61
	Day 14	**Day 30**	**Day 60**	**P-value**	
Atrophic scar	11.52±8.30	12.57±8.37	12.02±8.82	**0.018**[2]	
Hemoglobin	1.61±0.14[1*,11*,16*]	1.59±0.11[8*,13*,17*]	1.55±0.16[9*,14*,15*,19*]	**<0.001**[1]	
Melanin	0.58±0.06[1*,10*,15*]	0.57±0.07[8*,11*]	0.57±0.06[4*,9*,12*,15*]	**<0.001**[1]	
scale	5.98±4.15[4*]	6.93±4.17	6.66±4.46[5*]	**<0.001**[2]	
Texture	26.06±11.04	27.69±11.51	26.99±11.76	**0.036**[1]	

Repeated Measure Analysis, Post Hoc: LSD

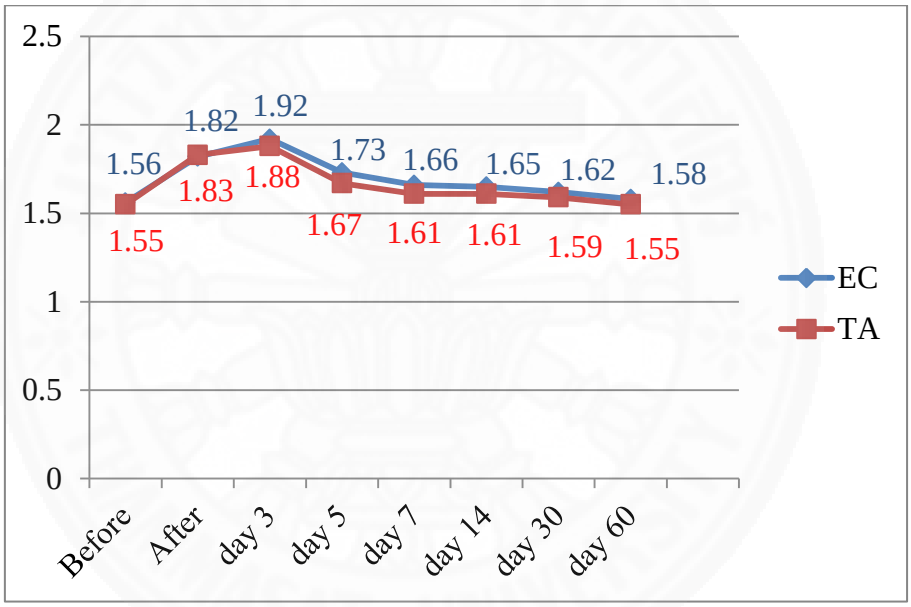
Friedman Test, Post Hoc: Wilcoxon Signed Ranks Test (P-value<0.002)

Table4.16 The biometric facial scan (Antera 3D) result of the side treated with the 0.02% TA cream

4.4.3 Comparison of both regimens

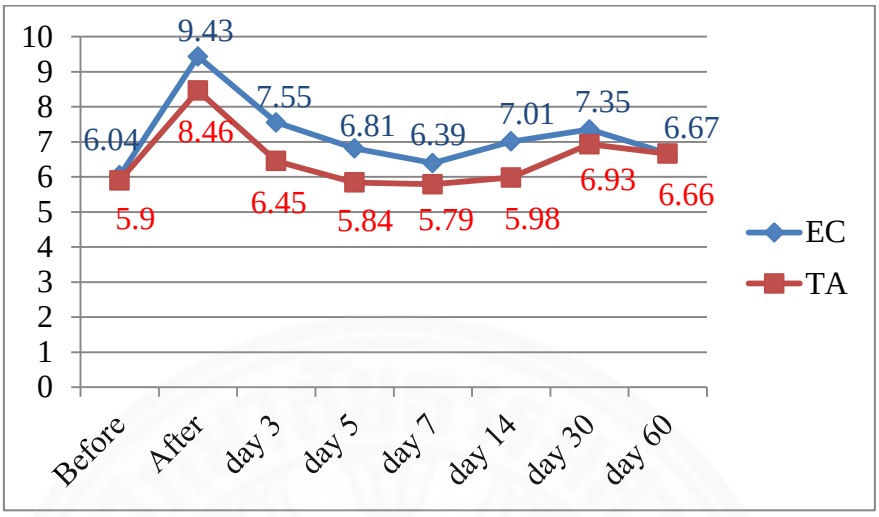
There was no significant difference in hemoglobin, scale, and melanin between the moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese and the 0.02% TA cream at any time point (p-value > 0.05). Moreover, no significant difference of skin texture, and atrophic scar volume was observed between the experimental cream and the 0.02% TA cream from baseline to day 60 (p-value > 0.05).

Table 4.17 The comparison of hemoglobin between both regimens evaluated by the Antera 3D device



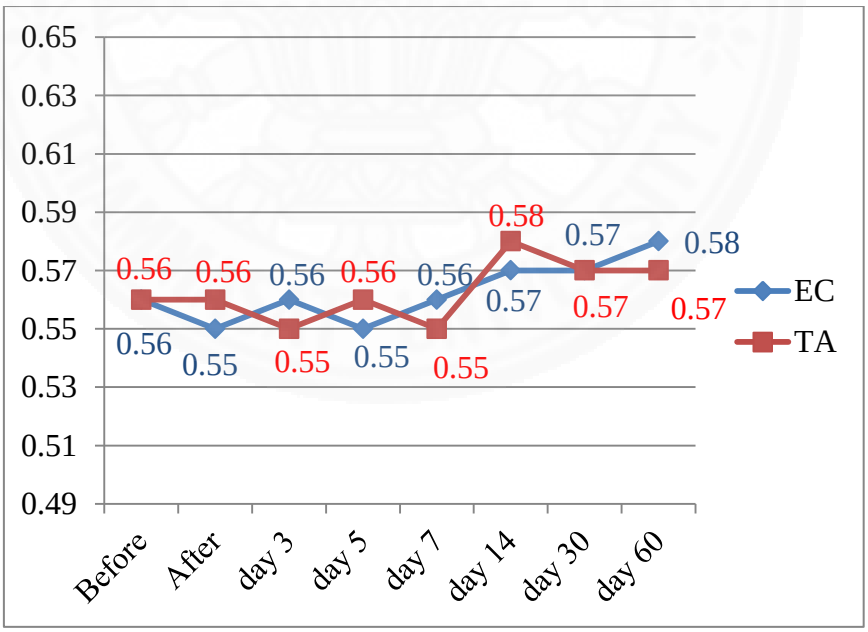
EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

Table 4.18 The comparison of scaling between both regimens evaluated by the Antera 3D device



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

Table 4.19 The comparison of melanin between both regimens evaluated by the Antera3D device



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

Variables	Before			After			Day 3			Day 5		
	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value
Atrophic scar	11.44±7.90	11.48±8.10	0.989[1]	12.48±9.03	11.26±8.61	0.589[2]	10.57±7.68	9.50±6.65	0.705[2]	11.81±9.17	10.62±7.53	0.766[2]
Hemoglobin	1.56±0.17	1.55±0.13	0.793[1]	1.82±0.13	1.83±0.14	0.846[1]	1.92±0.17	1.88±0.17	0.522[1]	1.73±0.16	1.67±0.14	0.261[1]
Melanin	0.56±0.07	0.56±0.07	0.725[1]	0.55±0.05	0.56±0.05	0.749[1]	0.56±0.06	0.55±0.05	0.462[1]	0.55±0.06	0.56±0.06	0.978[1]
scale	6.04±3.57	5.90±3.72	0.903[2]	9.43±5.14	8.46±5.10	0.482[2]	7.55±4.13	6.45±3.21	0.353[1]	6.81±4.78	5.84±3.61	0.705[2]
Texture	26.08±10.62	26.03±10.85	0.903[2]	28.42±12.40	26.70±11.83	0.507[2]	25.52±10.19	23.84±8.80	0.579[1]	26.81±12.30	24.86±10.18	0.797[2]

Variables	Day 7			Day 14			Day 30			Day 60		
	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value
Atrophic scar	12.21±9.84	10.93±7.89	0.892[2]	12.27±8.62	11.52±8.30	0.781[1]	13.19±8.93	12.57±8.37	0.820[1]	12.26±8.98	12.02±8.82	0.933[1]
Hemoglobin	1.66±0.16	1.61±0.14	0.340[1]	1.65±0.14	1.61±0.14	0.331[1]	1.62±0.15	1.59±0.11	0.381[1]	1.58±0.17	1.55±0.16	0.579[1]
Melanin	0.56±0.05	0.55±0.06	0.742[1]	0.57±0.07	0.58±0.06	0.719[1]	0.57±0.07	0.57±0.07	0.954[1]	0.58±0.06	0.57±0.06	0.948[1]
scale	6.39±4.11	5.79±3.88	0.640[1]	7.01±4.39	5.98±4.15	0.447[1]	7.35±4.08	6.93±4.17	0.752	6.67±4.16	6.66±4.46	0.968[2]
Texture	27.30±13.30	25.25±10.61	0.860[2]	27.29±11.61	26.06±11.04	0.734[1]	28.48±12.08	27.69±11.51	0.833[1]	27.39±12.16	26.99±11.76	0.914[1]

[1]Indepent T Test, [2]Mann-Whitney U Test

EC = experimental cream ,TA = 0.02% TA cream

Table4.20 The biometric facial scan (Antera 3D) result of the both regimens comparison

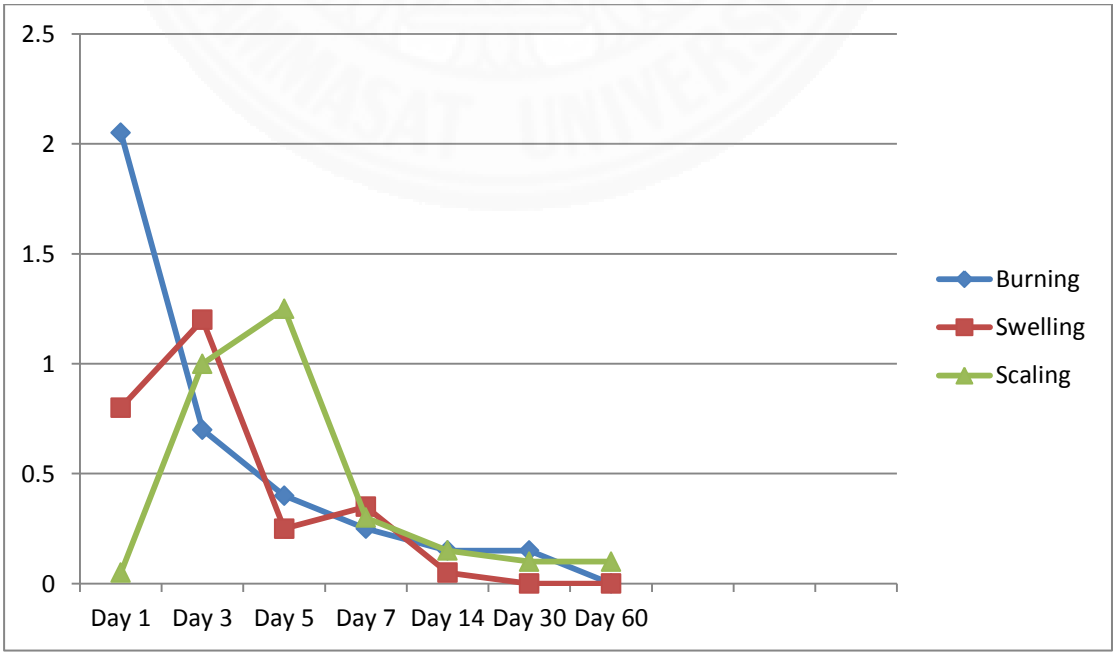
4.5 The wound healing and downtime evaluated by subjects

In every visit, the questionnaires mentioned of various post laser downtime had been provided to all subjects in a bid to assess the wound healing and downtime evaluated by the subject's view.

4.5.1 The side treated with the experimental cream

For the side treated with the experimental cream, burning feeling was certainly highest (2.05) at day 1 postoperatively and then significantly declined to 0.00 at day 60. Meanwhile, swelling and redness both reached their peak at day 3 (1.20 and 2.35 respectively) and then gradually dropped (to 0.00 and 0.05 respectively) at day 60. Crusting and scaling on the other hand, rose to the top at day 5 (1.50 and 1.25 respectively) and decreased to the lowest point (both 0.10) at day 60. Meanwhile, darkening skin was highest (1.60) at day 3 and then dropped down gradually. Otherwise, there was no significant change of acneiform eruption in this result.

Table 4.21 The changes of burning feeling, swelling, and scaling in the experimental cream treated side evaluated by the subject



(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

	Day 1	Day 3	Day 5	Day 7	Day 14	Day 30	Day 60	P-value
Burning	2.05±0.76	0.70±0.66	0.40±0.60	0.25±0.44	0.15±0.37	0.15±0.37	0.00±0.00	**<0.001**
Itching	0.10±0.31	0.70±0.67	0.75±0.64	0.55±0.51	0.30±0.47	0.15±0.37	0.10±0.31	**<0.001**
Swelling	0.80±0.77	1.20±1.06	0.25±0.55	0.35±0.67	0.05±0.22	0.00±0.00	0.00±0.00	**<0.001**
Redness	2.10±0.85	2.35±0.88	1.20±0.62	0.65±0.49	0.35±0.49	0.20±0.41	0.05±0.22	**<0.001**
Dryness	0.80±1.11	1.40±1.14	1.45±0.94	0.60±0.68	0.60±0.75	0.45±0.60	0.40±0.68	**<0.001**
Crusting	0.20±0.41	1.80±1.01	1.50±1.10	0.40±0.60	0.10±0.31	0.05±0.22	0.10±0.45	**<0.001**
Scaling	0.05±0.22	1.00±1.03	1.25±1.02	0.30±0.80	0.15±0.37	0.10±0.45	0.10±0.31	**<0.001**
Darkening	0.85±0.88	1.60±0.94	0.85±0.88	0.40±0.50	0.50±0.51	0.20±0.52	0.35±0.75	**<0.001**
Acneiform Eruption	0.05±0.22	0.10±0.31	0.00±0.00	0.15±0.37	0.15±0.37	0.10±0.31	0.00±0.00	0.318

Friedman Test, Post Hoc: Wilcoxon Signed Ranks Test (P-value<0.002)

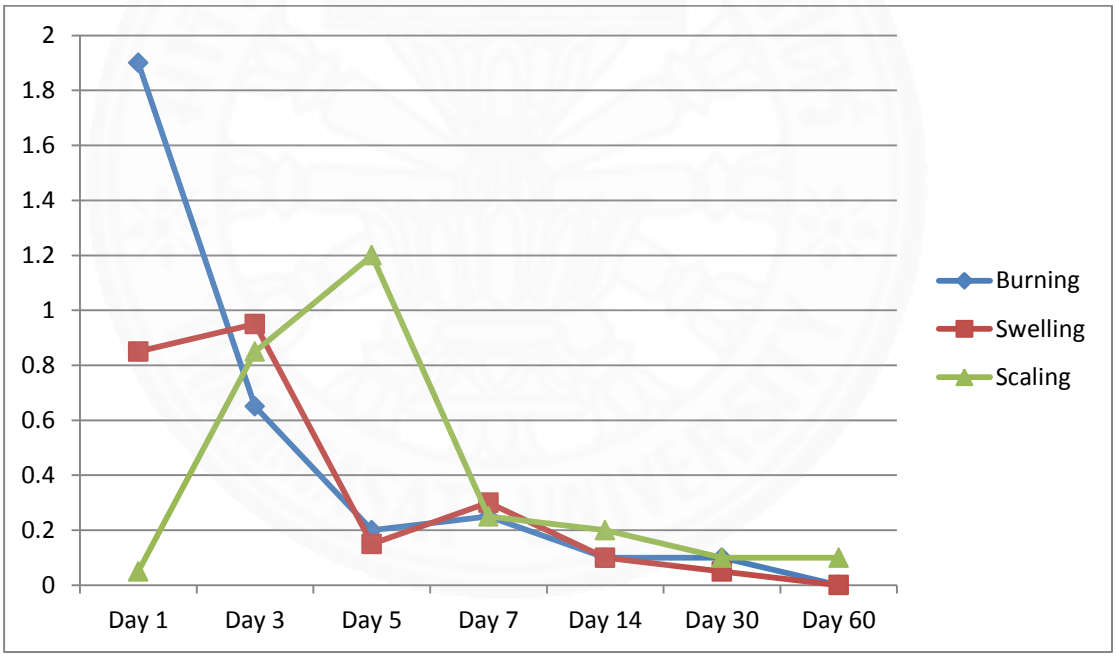
(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

Table4.22 The wound healing and downtimes evaluated by subjects on the side treated with the experimental cream

4.5.2 The side treated with the 0.02% TA cream

For the side treated with the 0.02% TA cream, burning feeling also reached the peak (1.90) at day 1 and then significantly dropped to 0.00 at day 60. In the same way, swelling and redness were both highest at day 3 (0.95 and 2.20 respectively) and then declined (to 0.00 and 0.05 respectively) at day 60. Moreover, crusting and scaling reached their peak at day 5 (1.45 and 1.20 respectively) and then dropped to the lowest point (both 0.10) at day 60. Finally, darkening skin rose to top (1.60) at day 3 and then also gradually declined down. Still, there was no significant change of acneiform eruption in this result.

Table 4.23 The changes of Burning feeling, swelling, and scaling in the 0.02% TA cream treated side evaluated by the subject



(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

	Day 1	Day 3	Day 5	Day 7	Day 14	Day 30	Day 60	P-value
Burning	1.90±0.91	0.65±0.75	0.20±0.41	0.25±0.55	0.10±0.31	0.10±0.31	0.00±0.00	<0.001
Itching	0.10±0.31	0.75±0.72	0.90±0.72	0.65±0.67	0.30±0.47	0.15±0.37	0.05±0.22	<0.001
Swelling	0.85±0.81	0.95±0.94	0.15±0.49	0.30±0.66	0.10±0.31	0.05±0.22	0.00±0.00	<0.001
Redness	2.00±0.79	2.20±0.89	1.00±0.73	0.65±0.59	0.20±0.41	0.15±0.37	0.05±0.22	<0.001
Dryness	0.80±1.11	1.50±1.28	1.45±0.89	0.65±0.67	0.55±0.83	0.35±0.59	0.40±0.68	<0.001
Crusting	0.20±0.41	1.55±1.00	1.45±1.00	0.30±0.66	0.15±0.37	0.10±0.45	0.10±0.45	<0.001
Scaling	0.05±0.22	0.85±0.88	1.20±1.06	0.25±0.64	0.20±0.41	0.10±0.45	0.10±0.31	<0.001
Darkening	0.90±0.91	1.60±0.82	0.85±0.81	0.35±0.49	0.50±0.51	0.20±0.52	0.35±0.75	<0.001
Acneiform Eruption	0.05±0.22	0.20±0.52	0.10±0.31	0.05±0.22	0.20±0.41	0.10±0.31	0.00±0.00	0.314

Friedman Test, Post Hoc: Wilcoxon Signed Ranks Test (P-value<0.002)

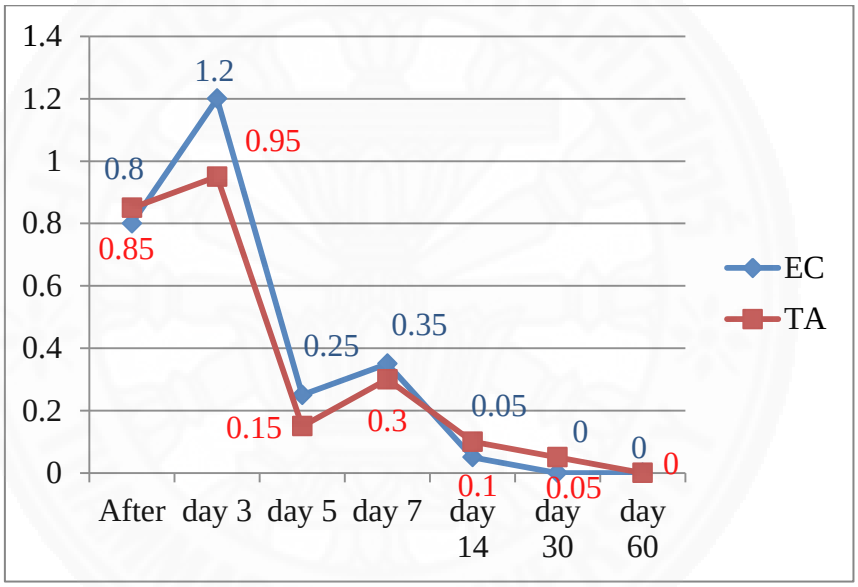
(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

Table4. 24 The wound healing and downtimes evaluated by subjects on the side treated with the 0.02% TA cream

4.5.3 Comparison of both regimens

Similar to the objective evaluation from the Antera scanning device, There was no significant difference in burning feeling, swelling, redness, crusting, scaling, and darkening skin between the moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese and the 0.02% TA cream at any time point (p-value > 0.05). Moreover, no significant difference of acneiform eruption was observed between the experimental cream and the 0.02% TA cream from baseline to day 60 (p-value > 0.05).

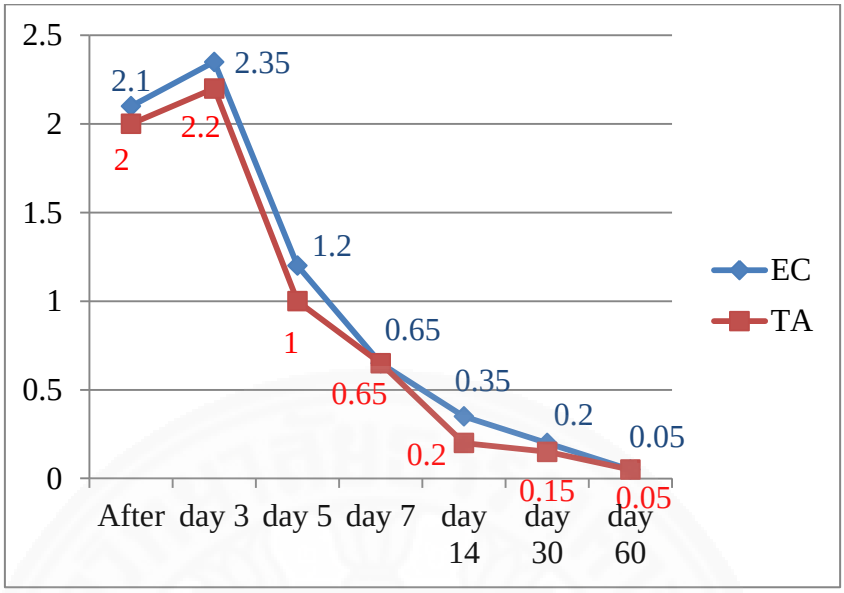
Table 4.25 The comparison of swelling between both regimens evaluated subjects



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

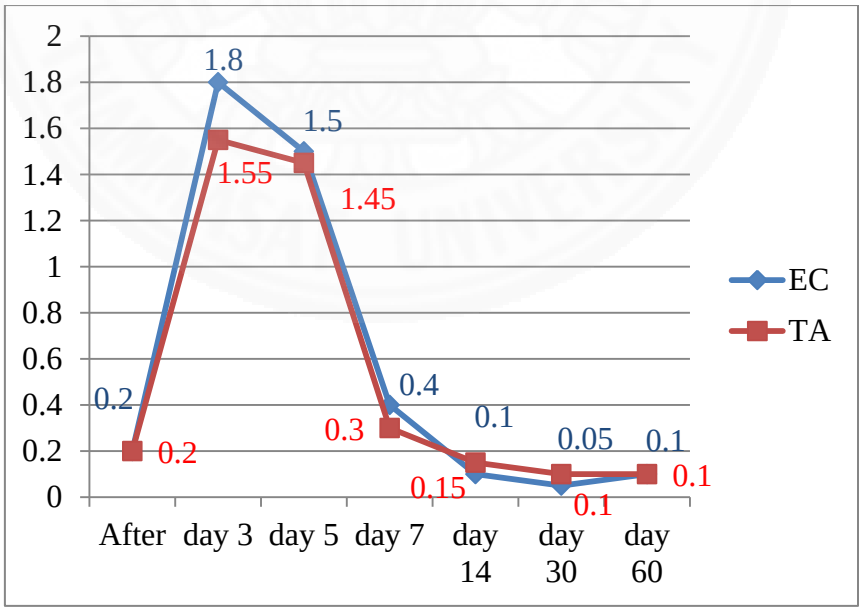
Table 4.26 The comparison of redness between both regimens evaluated subjects



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

Table 4.27 The comparison of crusting and scaling between both regimens evaluated subjects



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

Variables	Day 1			Day 3			Day 5		
	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value
Burning	2.05±0.76	1.90±0.91	0.475[2]	0.70±0.66	0.65±0.75	0.722[2]	0.40±0.60	0.20±0.41	0.265[2]
Itching	0.10±0.31	0.10±0.31	1.000[2]	0.70±0.67	0.75±0.72	0.916[2]	0.75±0.64	0.90±0.72	0.511[2]
Swelling	0.80±0.77	0.85±0.81	0.862[2]	1.20±1.06	0.95±0.94	0.395[2]	0.25±0.55	0.15±0.49	0.407[2]
Redness	2.10±0.85	2.00±0.79	0.638[2]	2.35±0.88	2.20±0.89	0.566[2]	1.20±0.62	1.00±0.73	0.367[2]
Dryness	0.80±1.11	0.80±1.11	1.000[2]	1.40±1.14	1.50±1.28	0.833[2]	1.45±0.94	1.45±0.89	0.943[2]
Crusting	0.20±0.41	0.20±0.41	1.000[2]	1.80±1.01	1.55±1.00	0.333[2]	1.50±1.10	1.45±1.00	0.954[2]
Scaling	0.05±0.22	0.05±0.22	1.000[2]	1.00±1.03	0.85±0.88	0.684[2]	1.25±1.02	1.20±1.06	0.819[2]
Darkening	0.85±0.88	0.90±0.91	0.874[2]	1.60±0.94	1.60±0.82	1.000[2]	0.85±0.88	0.85±0.81	0.919[2]
Acneiform Eruption	0.05±0.22	0.05±0.22	1.000[2]	0.10±0.31	0.20±0.52	0.604[2]	0.00±0.00	0.10±0.31	0.152[2]

Variables	Day 7			Day 14			Day 30			Day 60		
	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value	EC	TA	P-value
Burning	0.25±0.44	0.25±0.55	0.780[2]	0.15±0.37	0.10±0.31	0.637[2]	0.15±0.37	0.10±0.31	0.637[2]	0.00±0.00	0.00±0.00	1.000[2]
Itching	0.55±0.51	0.65±0.67	0.737[2]	0.30±0.47	0.30±0.47	1.000[2]	0.15±0.37	0.15±0.37	1.000[2]	0.10±0.31	0.05±0.22	0.553[2]
Swelling	0.35±0.67	0.30±0.66	0.739[2]	0.05±0.22	0.10±0.31	0.553[2]	0.00±0.00	0.05±0.22	0.317[2]	0.00±0.00	0.00±0.00	1.000[2]
Redness	0.65±0.49	0.65±0.59	0.912[2]	0.35±0.49	0.20±0.41	0.294[2]	0.20±0.41	0.15±0.37	0.681[2]	0.05±0.22	0.05±0.22	1.000[2]
Dryness	0.60±0.68	0.65±0.67	0.787[2]	0.60±0.75	0.55±0.83	0.725[2]	0.45±0.60	0.35±0.59	0.539[2]	0.40±0.68	0.40±0.68	1.000[2]
Crusting	0.40±0.60	0.30±0.66	0.387[2]	0.10±0.31	0.15±0.37	0.637[2]	0.05±0.22	0.10±0.45	0.917[2]	0.10±0.45	0.10±0.45	1.000[2]
Scaling	0.30±0.80	0.25±0.64	0.965[2]	0.15±0.37	0.20±0.41	0.681[2]	0.10±0.45	0.10±0.45	1.000[2]	0.10±0.31	0.10±0.31	1.000[2]
Darkening	0.40±0.50	0.35±0.49	0.747[2]	0.50±0.51	0.50±0.51	1.000[2]	0.20±0.52	0.20±0.52	1.000[2]	0.35±0.75	0.35±0.75	1.000[2]
Acneiform Eruption	0.15±0.37	0.05±0.22	0.298[2]	0.15±0.37	0.20±0.41	0.681[2]	0.10±0.31	0.10±0.31	1.000[2]	0.00±0.00	0.00±0.00	1.000[2]

[1]Indepent T Test, [2]Mann-Whitney U Test

EC = experimental cream, TA = 0.02% TA cream

(0 = no symptom, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)

Table4.28 The wound healing and downtimes evaluated by subjects; the comparison of bothregimens

4.6 Patient satisfaction

We used the questionnaires to evaluate the patient satisfaction at day 30 and day 60 post irradiation. The result was classified into two categories; the laser treatment result and the post treatment regimen

4.6.1 The laser treatment result

For the patient satisfaction of the laser treatment result, average scores for the overall result were 2.6 at day 30 and 2.35 at day 60, which both were rated as a moderate improvement. Besides, other parameters including acne scar result, pores result, red spot, and dark spot were rated as a little improvement to moderate improvement. By the way, there was no significant difference between the laser treatment result at both day 30 and day 60 for all parameters (p-value > 0.05).

Table 4.29 Patient satisfaction for the laser treatment result

Parameters	**Day 30**	**Day 60**	**P-value**
Acne scar result	2.15	1.95	0.206
Pores result	2.25	2.05	0.357
Red spot	2.25	1.75	0.167
Dark spot	1.95	1.55	0.128
Overall result	2.60	2.35	0.096

Wilcoxon Signed Ranks Test

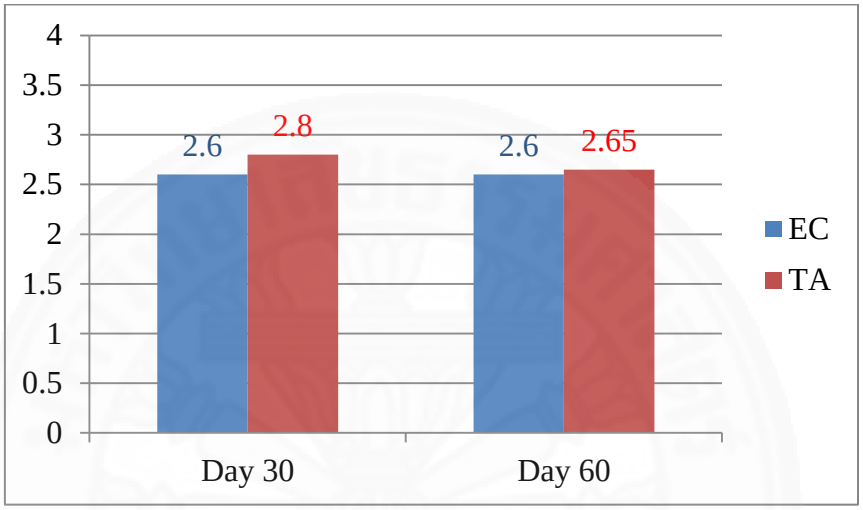
0 = no change observed, 1 = a little improvement, 2 = moderate improvement, 3 = a lot improvement, 4 = very improvement

4.6.2 The post treatment regimen

For the patient satisfaction of the post treatment regimen, the average scores of the experimental cream were both 2.6 (moderate satisfaction) at day 30 and day 60. Meanwhile, the average scores of 0.02% TA cream were 2.80 at day 30, and 2.65 at day 60 which both were rated as a moderate satisfaction as well. Whilst, at day 30, most subjects rated the satisfaction level as a lot satisfaction for both the experimental cream (50%) and 0.02% TA cream (70%). On the other hand, at day 60,

most subjects rated the satisfaction level for the experimental cream as a lot satisfaction (35%), but moderate satisfaction (40%) for the 0.02% TA cream. By the way, there was no significant difference between the patient satisfaction of the experimental cream and 0.02% TA cream at any time point (p-value > 0.05).

Table 4.30 Patient satisfaction for the post treatment regimen



EC = experimental cream, TA = 0.02% TA cream, (p-value > 0.05)

0 = no satisfaction, 1 = a little satisfaction, 2 = moderate satisfaction, 3 = a lot satisfaction, 4 = very satisfaction

Table 4.31 Patient satisfaction for the post treatment regimen (in details)

Satisfaction	**Day 30**			**Day 60**		
	EC	**TA**	**P-value**	**EC**	**TA**	**P-value**
Average score	2.60	2.80	0.325	2.60	2.65	0.921
Very satisfaction(4)	2 (10.0)	2 (10.0)	0.401	4 (20.0)	5 (25.0)	0.842
A lot satisfaction(3)	10 (50.0)	14 (70.0)		7 (35.0)	5 (25.0)	
Moderate satisfaction(2)	6 (30.0)	2 (10.0)		6 (30.0)	8 (40.0)	
A little satisfaction(1)	2 (10.0)	2 (10.0)		3 (15.0)	2 (10.0)	
No satisfaction(0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Mann-Whitney U Test, Fisher's Exact Test

EC = experimental cream, TA = 0.02% TA cream

0 = no satisfaction, 1 = a little satisfaction, 2 = moderate satisfaction, 3 = a lot satisfaction, 4 = very satisfaction

4.7 Dermatology quality of life index

There were significant improvements for the question 2, 3, and 4 as the following details. The question 2 was "over the last week, how embarrassed or self-conscious have you been because of your skin?" and the answer for "not at all" was significantly changed from 35% to 80%. Meanwhile in the question 3, "over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?" the answer for "a lot" was changed from 35% to 0%, and the answer for "not at all" was increased from 25% to 65%. Finally, the question 4 "over the last week, how much has your skin influenced the clothes you wear?" the answer for "not at all" had increased from 30% to 70%. Meanwhile, the other questions remained no significant changes for the answer (p-value > 0.05).

Table 4.32 Dermatology quality of life index (DQLI) result

Question	**Before**	**After**	**P-value**
1. Over the last week, how itchy, sore, painful or stinging has your skin been?			0.835
Very much	0 (0.0)	0 (0.0)	
A lot	1 (5.0)	1 (0.0)	
A little	6 (30.0)	4 (20.0)	
Not at all	13 (65.0)	15 (75.0)	
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?			0.028
Very much	2 (10.0)	0 (0.0)	
A lot	5 (25.0)	2 (10.0)	
A little	6 (30.0)	2 (10.0)	
Not at all	7 (35.0)	16 (80.0)	
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or			0.007

Question	Before	After	P-value
garden?			
Very much	0 (0.0)	1 (5.0)	
A lot	7 (35.00	0 (0.0)	
A little	5 (25.0)	3 (15.0)	
Not at all	5 (25.0)	13 (65.0)	
Not relevant	3 (15.0)	3 (15.0)	
4. Over the last week, how much has your skin influenced the clothes you wear?			0.003
Very much	0 (0.0)	0 (0.00	
A lot	2 (10.0)	0 (0.0)	
A little	7 (35.0)	0 (0.00	
Not at all	6 (30.0)	14 (70.0)	
Not relevant	5 (25.0)	6 (30.0)	
5. Over the last week, how much has your skin affected any social or leisure activities?			0.060
Very much	2 (10.0)	0 (0.0)	
A lot	4 (20.0)	0 (0.0)	
A little	1 (5.0)	4 (20.0)	
Not at all	9 (45.0)	13 (65.0)	
Not relevant	4 (20.0)	3 (15.0)	
6. Over the last week, how much has your skin made it difficult for you to do any sport?			0.823
Very much	0 (0.0)	1 (5.0)	
A lot	2 (10.0)	2 (10.0)	
A little	3 (15.0)	1 (5.0)	
Not at all	12 (60.0)	14 (70.0)	
Not relevant	3 (15.00	2 (10.00	
7. Over the last week, has your skin prevented you from working or studying?			1.000
Yes	0 (0.0)	0 (0.0)	
No	17 (85.0)	17 (85.0)	
Not relevant	3 (15.0)	3 (15.0)	
If "No", over the last week how much has your skin been a problem at work or studying?			0.103
A lot	1 (5.9)	0 (0.0)	
A little	3 (17.9)	0 (0.0)	
Not at all	13 (76.5)	17 (100.0)	
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?			0.061

Question	Before	After	P-value
Very much	0 (0.0)	0 (0.0)	
A lot	1 (5.0)	0 (0.0)	
A little	6 (30.0)	1 (5.0)	
Not at all	10 (50.0)	17 (85.0)	
Not relevant	3 (15.0)	2 (10.0)	
9. Over the last week, how much has your skin caused any sexual difficulties?			0.451
Very much	0 (0.0)	0 (0.0)	
A lot	0 (0.0)	0 (0.0)	
A little	1 (5.0)	0 (0.0)	
Not at all	14 (70.0)	17 (85.0)	
Not relevant	5 (25.0)	3 (15.00	
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?			0.254
Very much	0 (0.0)	0 (0.0)	
A lot	1 (5.0)	0 (0.0)	
A little	4 (20.0)	1 (5.0)	
Not at all	12 (60.0)	17 (85.0)	
Not relevant	3 (15.0)	2 (10.0)	

4.8 The assessment of sunscreen knowledge

We used many questions to evaluate the subject's knowledge about sun protection and sunscreen. The result was shown below.

Table 4.33 The result for the assessment of sunscreen knowledge

Question	Number	Percentage
History of sun avoidance and sun protection		
What is the average time/day you spend outdoor at 10.00 AM to 4.00 PM?		
Less than 30 min/day	9	45.0
30 min – 1 hr/day	9	45.0
1-2 hr/day	2	10.0
At least 3 hr/day	0	0.0
In the last 12 months, how many times did you have burn skin?		
None	12	60.0
1 time	3	15.0

Question	Number	Percentage
2 times	3	15.0
3 times	0	0.0
4 times or more	2	10.0
Do you wear sunscreen before expose to sunlight?		
Never	6	30.0
Rarely	4	20.0
Sometimes	5	25.0
Often	1	5.0
Always	4	20.0
Do you wear a hat before expose to sunlight?		
Never	9	45.0
Rarely	8	40.0
Sometimes	3	15.0
Often	0	0.0
Always	0	0.0
Do you go indoor for sun avoidance?		
Never	4	20.0
Rarely	3	15.0
Sometimes	6	30.0
Often	7	35.0
Always	0	0.0
Do you use an umbrella for sunlight protection?		
Never	8	40.0
Rarely	3	15.0
Sometimes	4	20.0
Often	4	20.0
Always	1	5.0
Do you wear sunglasses?		
Never	12	60.0
Rarely	3	15.0
Sometimes	4	20.0
Often	1	5.0
Always	0	0.0
Which type of sunscreen is the best?		
UVA protection	5	25.0
UVB protection	0	0.0
Both UVA and UVB protection	9	45.0
Not sure	6	30.0
How much SPF should be included in the sunscreen?		
<30	1	5.0
30-50	9	45.0

Question	Number	Percentage
>50	5	25.0
Not sure	5	25.0
How much PA should be included in the sunscreen?		
PA+	2	10.0
PA++	4	20.0
PA+++	7	35.0
Not sure	7	35.0
How much quantity of the sunscreen should you wear over the face for one time use?		
One pinhead	3	15.0
Half a finger bred	8	40.0
One finger bred	2	10.0
Two finger breds	2	10.0
Not sure	5	25.0
When should you wear sunscreen?		
Only indoor time	0	0.0
Only outdoor time	14	70.0
Everyday	4	20.0
Not sure	2	10.0
What is the proper time to wear sunscreen?		
Just before going outdoor	2	10.0
5-10 min before going outdoor	9	45.0
20-30 min before going outdoor	6	30.0
Not sure	3	15.0
Should you re-apply the sunscreen after the first wearing?		
No, never	12	60.0
One time re-apply when going outdoor	1	5.0
Re-apply every 2 hrs when going outdoor	2	10.0
Re-apply anytime you want	3	15.0
Not sure	2	10.0
What is the purpose of sun protection?		
Protect the skin from burn and tanning	14	70.0
Prevent melasma and freckle	6	30.0
Prevent aging	5	25.0
Prevent skin cancer	7	35.0
How to prevent post-laser side effects		
Normally, Do you wear sunscreen after undergoing facial laser?		
Yes	12	60.0
No	8	40.0

Question	Number	Percentage
Not sure	0	0.0
Do you always wear sunscreen for at least 4-6 weeks after undergoing facial laser?		
Yes	6	30.0
No	14	70.0
Not sure	0	0.0
Do you use an anti-inflammatory topical drug after undergoing facial laser?		
Yes	5	25.0
No	14	70.0
Not sure	1	5.0
Do you use sun protection equipment such as a cap or an umbrella after undergoing facial laser?		
Yes	13	65.0
No	6	30.0
Not sure	1	5.0
When is the proper time should you wear the sunscreen after undergoing facial laser?		
Immediately after undergoing laser	8	40.0
The next morning after undergoing laser	10	50.0
3 days after undergoing laser	1	5.0
After the downtimes are recovered	0	0.0
Not sure	1	5.0

4.9 Pain score from the laser procedure

For the pain score from the laser procedure, we used the 0 to 10 pain scoring system which 0 mean no painful, and 10 mean the most painful experience in life. The result came out that average scores were 6.95. Most subjects (40%) rated the pain as 7 scores. By the way, one subject rated the pain as 10 scores. The pain score from the laser procedure were shown in the table below.

Table 4.34 The result for the pain score from the laser procedure

Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Number	0	0	0	0	0	2	5	8	3	1	1
%	0.00	0.00	0.00	0.00	0.00	10.00	25.00	40.00	15.00	5.00	5.00

Average score = 6.95

4.10 Side effect

Beyond of the downtime normally observed post-operatively including redness, swelling, crusting, scaling, and pigmentation, 1 (5%) of 20 patients developed acneiform eruption on both sides of the face at day 3 post irradiation. Besides, there was no serious side effect observed in this study.

4.11 Discussion

For the clinical assessment by the expert panel, the result showed that the experimental cream had the comparable efficacies with 0.02% TA cream to decrease post-laser downtime and side effects. In details, both the experimental cream and 0.02% TA cream were able to decrease redness and swelling in 5 days, and decrease scaling and crusting in 7 days respectively. Nevertheless, PIH were observed at day 14 for both regimens treated side. They were only averagely rated as minimal intensity from day 14 until the end of the study and their incidence was not different between the regimens.

On the other hand, the expert panel assessment of the laser treatment result showed us that the average score was rated as “not change”. This was reasonable because the indication of the $FrCO_2$ laser is acne scar treatment, which often requires several sessions of the procedure to see the obvious result. Moreover, the previous study showed us that it required at least 3 months (longer than our study period) to see the improvement of the acne scar result after one time $FrCO_2$ irradiation (8). Nevertheless, for the patient satisfaction, it turned out that the subject averagely rated the overall result as moderate improvement.

For an objective evaluation in our study, we used the biometric facial scan (Antera 3D) to assess the improvement of post-laser downtime and wound healing process. The result revealed that both the experimental cream containing anti-inflammatory ingredients and 0.02% TA cream significantly decreased hemoglobin (redness) and scale with no different efficacies among the products. Melanin, although had no significant change, had a tendency to rise up a bit at day 14 until the end of the study (day 60). When considering it with the clinical result which the

expert panel assessment revealed that most subjects developed PIH at 2 weeks post-operatively, and the demographic data which showed that most subjects had dark skin which has a tendency to develop PIH (4), it can be explained that this pattern of melanin rising was in part of the PIH development process. Even though, we had provided the anti-inflammatory agents (both the experimental cream and 0.02% TA cream) to all subjects, and they both improved the other downtime but still, PIH developed. To explain this, there were many factors in our study that favored PIH development. First, most subjects had dark skin phototype. Second, the $FrCO_2$ itself, normally cause post-operative downtime including PIH (the incidence of the PIH following AFR in patient with skin phototype IV is as high as 92%) (3), and finally, the subject's knowledge for sun avoidance and sun protection were inadequate. Apparently, the result for an assessment of sunscreen knowledge showed us that 30% of the subject had never worn sunscreen before and most subjects had never used sun-protection equipment such as a hat or an umbrella.

However, comparing with previous studies, the one conducted by Manuskiatti et al. in 2010 developed 92% PIH (3) which was very high due to couple reasons; first, the study was conducted in dark skin patient, second, they conducted 3 sessions of $FrCO_2$ which could have favored more PIH, and third, they used petrolatum alone as a post-treatment regimen. Another study conducted by Cheyasak et al. in 2015 developed 75% PIH in the petrolatum treated side and 40% PIH in the steroid treated side (8). In that study, the author used topical high potency steroid 0.05% Clobetasol propionate for 2 days as a treatment for reducing post-laser PIH. The incidence of 40% PIH on the high potency steroid treated side was significantly better than the incidence of 75% PIH in the control group. Unfortunately, 2 patients developed acneiform eruption specifically on the high potency steroid treated side at the third day post-operatively which could be steroid acne.

In our study, the incidence of PIH was 60% on the experimental cream treated side. In other words, this moisturizer containing anti-inflammatory ingredients yielded better efficacy than petrolatum for a reduction of post-laser PIH, but not as good as high potency steroid 0.05% Clobetasol propionate. However, when considering about the side effect, it turned out that our experimental cream produced

Table 4.35 Comparison between our study and the previous studies

The author	Laser	Laser parameter	Sample size	Study period	Post-treatment regimen	Duration of applying	Incidence of PIH	Intensity of PIH	Other S/E
Manuskiatti et al. (3)	$FrCO_2$ X3 sessions	49 MTZ/cm^2 density, 9.6% skin surface coverage, 500 µm beam size, 75-105 mJ/MTZ pulse energies	13	6 months	Petrolatum	7 days	92%	mild	4 cases of acneiform eruption, 2 cases of ACD, 1 case of herpes simplex infection
Cheyasak et al. (8)	$FrCO_2$ 1 session	Single pass, 5% skin surface coverage, 950 µs pulse duration, 12.75 mJ pulse energy	40	3 months	0.05% clobetasol propionate + petrolatum	CP x 2 days PT x 5 days	40%	minimal	2 cases of steroid acne
					Petrolatum (control)	7 days	75%	minimal	1 case of acneiform eruption
Our study	$FrCO_2$ 1 session	2 passes of 100 MTZ/cm^2 density, less than 15% coverage, 120 µm beam size, 30 w peak power, 50 mj pulse energy	20	2 months	The experimental cream	7 days	60%	minimal	1 case of laser provoke acneiform eruption
					0.02% TA cream (control)	7 days	55%	minimal	

CP = 0.05% clobetasol propionate, PT = petrolatum, ACD = allergic contact dermatitis

lower incidence of side effect than 0.05% Clobetasol propionate. In details, 1 patient in our study developed acneiform eruption at day 3 post irradiation. This eruption was probably not caused from one of our post-treatment regimens due to its both sides pattern of eruption and it was later subside along with the continue using of both post-treatment regimens. Moreover, the steroid used in our study was just the low potency which was unlikely to cause acneiform eruption at the third they after using. Thus, this eruption should be caused by the $FrCO_2$ laser itself which normally has a chance to provoke acne. In conclusion, our study had much lower incidence of side effects compared to those in the previous studies (3, 8) and the incidence of PIH on our experimental cream treated side was also not different from those on the 0.02% TA cream treated side or our control side (60% and 55% respectively at day 60, with p-value > 0.05).

The low incidence of PIH and the improvement of other downtime in the experimental cream treated side can be explained by the positive effects of its active ingredients. Typically, panthenol itself maintains an anti-inflammatory effect crucial to prevent PIH caused by the increasing of melanin distribution and melanin production from various released inflammatory mediators, such as prostaglandin E2, D2, leukotriene C4, D4, and thromboxane-2 (6). Additionally, panthenol also improves skin barrier by decreasing TEWL and maintaining skin softness (13), consistent with the improved scaling in our study. In the meantime, madecassoside modulates the inflammatory mediators and stimulates collagen expression (15, 16). Finally, copper-zinc-manganese complexes are the trace elements for skin function improvement by regulating keratinocyte proliferation (34) related to the wound healing process and scale-crust improvement in this study. In conclusion, overall positive effects of this experimental cream were the anti-inflammatory and moisturizing effects that help improving wound healing process and decreasing post-laser downtime.

For a subjective evaluation, we used the questionnaires to assess the wound healing and downtime evaluated by subjects. The result revealed that both the experimental cream containing anti-inflammatory ingredients and 0.02% TA cream significantly improved burning feeling, redness, swelling, dryness, scaling and crusting, with no different efficacies among the products. These results were also

consistent with the objective evaluation and the clinical assessed by the expert panel assessment of the photography.

Moreover, we used the questionnaires to assess patient satisfaction for the laser treatment result and the post-treatment regimens. For the satisfaction of the laser treatment result, it revealed that the average satisfaction level were moderate satisfaction at both day 30 and day 60. On the other hand, for the satisfaction of the post-treatment regimen, both the experimental cream and 0.02% TA cream were averagely rated as moderate satisfaction. There was no difference in the satisfaction level between the regimens.

A recent study conducted by Cheyasak et al. in 2015 revealed that short-term application of high potency topical steroid 0.05% Clobetasol propionate for only 2 days after treatment decreased the risk of PIH and other downtime following AFR (8). However, there were 2/40 subjects developed acneiform eruption on the high potency steroid treated side which could be steroid acne. As a consequence, we used the low potency topical steroid 0.02% TA cream as a control instead to avoid adverse effects from the high potency steroid. Thus, our study revealed that, with the low potency steroid and the moisturizer with anti-inflammatory ingredients, our subject developed lower incidence of side effect. In addition, the moisturizer with anti-inflammatory ingredients and the low potency steroid used in our study effectively decreased the downtime and improved the wound healing process after AFR with the comparable efficacy. In details, both regimens improved swelling and redness in 3-5 days and immediately improved crusting and scaling after day 5. When compared these efficacies with those from the high potency steroid and petrolatum in the previous study, apparently our experimental cream had the compatible efficacies with those regimens to improve wound healing and downtime.

Table 4.36 The improved wound healing and downtime in the previous study (8)

	Clobetasol + petrolatun Mean ± SD	Petrolatum only Mean ± SD	*p*-value
Pain, hour	11.4 ± 12.1	15.6 ± 19.2	0.004
Crusting, day	6.1 ± 2.9	6.5 ± 2.9	0.035
Erythema, day	4.5 ± 3.9	4.8 ± 3.4	0.089
Oedema, day	1.7 ± 1.1	2.0 ± 1.3	0.017

Therefore, this moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese yielded comparable efficacies to the 0.02% TA cream for decreasing post-laser downtime and improving wound healing process. Moreover, it was safe and produced minimal side effect. Hence, the applying of non-steroidal anti-inflammatory moisturizer in our study could be a novel treatment modality to decrease post-ablative laser downtime and to avoid adverse effects from the steroid, leading to wound healing process improvement.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusion

Moisturizer containing anti-inflammatory ingredients including 5% panthenol, madecassoside, and copper-zinc-manganese has the comparable efficacy to 0.02% TA cream for decreasing post-ablative laser downtime, lowering incidence of PIH and improving wound healing process.

This moisturizer containing anti-inflammatory ingredients could be a novel treatment modality for the reduction of post-ablative laser downtime by using non-steroidal anti-inflammatory agents in a bid to avoid adverse effects from steroids and improve wound healing process.

5.2 Recommendations

Further, this moisturizer could be applied for the treatment of various inflammatory skin conditions due to its comparable efficacies with the 0.02% TA cream which is widely use for the treatment of many inflammatory skin conditions as well.

Nevertheless, there were some limitations in our study including small sample size, short period of follow up, and only the study in Asian population with skin phototype IV. Thus, more sample size, more skin color variation, and a longer study period are suggested to obtain more accurate treatment results of this non-steroidal anti-inflammatory moisturizer to improve the wound healing process and decrease the downtime after AFR.

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APPENDICES

APPENDIX A
CASE RECORD FORM

Case Record Form

ข้อมูลทั่วไปของผู้ป่วย (Patient demographic Information)

1. เพศ O 1. ชาย O 2. หญิง

2. วัน/เดือน/ปีเกิด ……/……/……

3. อายุ .....ปี ……เดือน

4. อาชีพ O 1. นักเรียน/นักศึกษา O 2. พนักงาน/ลูกจ้าง O 3. แม่บ้าน O 4.ข้าราชการ O 5. กิจการส่วนตัว

O 6. อื่นๆ โปรดระบุ……..

5. โรคประจำตัว O 1. ไม่เป็น O 2. เป็น (ระบุโรค.....)

5.1 การรักษาที่เคยได้รับ……

5.2 การรักษาที่ได้รับในปัจจุบัน……..

6. โรคเกี่ยวกับผิวหนัง

O 1. ไม่เป็น

O 2. เป็น โปรดระบุชนิดของโรค (ตอบได้มากกว่า 1 ข้อ)

O สิว O ฝ้า O กระ O ผิวหนังอักเสบ O ภูมิแพ้

O อื่นๆ (โปรดระบุ)……

6.2 การรักษาที่เคยได้รับ (ตอบได้มากกว่า 1 ข้อ)

O ยาทา O ยากิน O เลเซอร์ O อื่นๆ (โปรดระบุ)……..

6.3 การรักษาที่ได้รับในปัจจุบัน (ตอบได้มากกว่า 1 ข้อ)

Oยาทา Oยากิน O เลเซอร์ Oอื่นๆ (โปรดระบุ)……

7. ประวัติแพ้ยา O 1. ไม่มี O 2. มี

(โปรดระบุยา.....และอาการแสดง.....)

8. ประวัติได้รับแสงแดดจัดตอนช่วงกลางวัน ใน 1 วัน

O 1. น้อยกว่า 30 นาที O 2. ครึ่งชั่วโมงถึง 1 ชั่วโมง O 3. 1-2 ชั่วโมง O 4. มากกว่า 2 ชั่วโมง

9. ปัจจัยกระตุ้นที่ให้ผิวสูญเสียน้ำ (ตอบได้มากกว่า 1 ข้อ)

O 1.อาบน้านานกว่า 10 นาที O 2. อาบน้ามากว่า 2 ครั้งต่อวัน O 3. อาบน้าอุ่น O 4. อยู่ในห้องที่เปิดแอร์มากกว่า 6 ชั่วโมงต่อวัน

10. ประวัติการใช้ครีมกันแดดบนใบหน้า

O 1. ใช้ทุกวัน ตอนเช้าและเที่ยง O 2.ใช้ทุกวัน ตอนเช้าเท่านั้น

O 3. ใช้ บ้างเป็นบางวัน O 4.ไม่ได้ใช้ O 5. ใช้ในเวลาอื่นๆ ระบุ .....

10.1 ชื่อผลิตภัณฑ์ครีมกันแดดที่ใช้ (โปรดระบุ).....

11. ผลิตภัณฑาความสะอาดใบหน้าที่ใช้

O 1. สบู่ก้อน O 2. สบู่เจลเหลว O 3. ครีมโฟม O 4. น้าเปล่า

12. ประวัติการใช้โทนเนอร์ใสเช็ดหลังล้างหน้า (facial toner)

O 1. ไม่ได้ใช้ O 2. ใช้ O 3. เคยใช้

13. ประวัติการใช้ครีมรองพื้น/ครีมปกปิดริ้วรอย

O 1. ใช้ทุกวัน O 2.ใช้ 2-3 วัน / สัปดาห์ O 3. ใช้ 1 วัน / สัปดาห์

O 4.ใช้ 2-3 ครั้ง / เดือน O 5.ใช้ 1 ครั้ง / เดือน O 6.ไม่ได้ใช้

14. ประวัติการใช้ครีมลดเลือนริ้วรอย O 1. ไม่ใช้ O 2. ใช้ O3.เคยใช้

15. ประวัติการใช้ครีมยกกระชับใบหน้า O 1. ไม่ใช้ O 2. ใช้ O3.เคยใช้

16. ประวัติการใช้ครีมกระชับรูขุมขน O 1. ไม่ใช้ O 2. ใช้ O3.เคยใช้

17. ประวัติการใช้ครีมกรดผลไม้ O 1. ไม่ใช้ O 2. ใช้ O3.เคยใช้

18. ประวัติการใช้ครีมวิตามินเอ O 1. ไม่ใช้ O 2. ใช้ O3.เคยใช้

19. ประวัติการใช้ครีมละลายหัวสิวก่อนล้างหน้า O 1. ไม่ใช้ O 2. ใช้ O3.เคยใช้

20. ประวัติการทำทรีทเม้น นวดหน้า (facial treatment)

O 1. ไม่เคย

O 2.เคย โปรดระบุชนิด (ตอบได้มากกว่า 1 ข้อ)

O AHA O Ionto O Phono Oกรอผิว Oอื่นๆ โปรดระบุ .....

21. ประวัติการทาเลเซอร์ผิวหน้า

O 1. ไม่เคย

O 2. เคย โปรดระบุชนิด (ตอบได้มากกว่า 1 ข้อ)

O IPL O CO2 O Qs NdYag O Long pulse O Nd Yag O Erbium

O Radiofrequency (RF) Oอื่นๆ โปรดระบุ .....

22. ประวัติเข้ารับการฉีดสารเติมเต็ม (filler) ที่ใบหน้า

O 1. ไม่เคย

O 2. เคย (โปรดระบุบริเวณ……และจานวนครั้ง……., ฉีดไปแล้วนาน.....เดือน.....ปี)

23. ประวัติการฉีดโบทอกซ์ที่ใบหน้า

O 1. ไม่เคย

O 2. เคย (โปรดระบุบริเวณ.....และจานวนครั้ง....., ฉีดไปแล้วนาน.....เดือน.....ปี)

24. ประวัติการรับประทานยากลุ่มวิตามินเอ

O 1.ไม่เคยทาน

O 2. ทานอยู่

O 3. เคยทาน (ทานไปแล้วนาน.....เดือน.....ปี)

25. ลักษณะของผิวหน้าท่าน ตามความคิดของท่าน

O1. ผิวมัน O2. ผิวผสม O3. ผิวแห้ง

26. ลักษณะความมันของผิวหน้า ตามความคิดของท่าน

O1. มันมาก O2. มันเฉพาะหน้าผาก, จมูกและคาง O3.ไม่มัน

27. ลักษณะของสีผิว

O 1. ผิวขาว O2. ผิวขาวเหลือง O3. ผิวสองสี O4. ผิวคล้ำดา

28. ประวัติการตั้งครรภ์ (ตอบเฉพาะผู้หญิง)

O 1. กาลังตั้งครรภ์ O 2. ไม่ได้ตั้งครรภ์ O 3. ไม่แน่ใจ

29. ประวัติให้นมบุตร (ตอบเฉพาะผู้หญิง)

O 1. กาลังให้นมบุตร O 2. ไม่ได้ให้นมบุตร

APPENDIX B
EXPERT PANEL ASSESSMENT OF THE PHOTOGRAPHY

Expert panel assessment: Side effects

ผู้ประเมิน _____

การเปรียบเทียบผลการรักษาและผลข้างเคียงต่างๆ เทียบกับหลังรักษาด้วยเลเซอร์ทันที

Subject No. _____

__B _day 1 _day 3 _day 5 __day7 __day14 __day30 __day60

	ใบหน้าด้านซ้าย						ใบหน้าด้านขวา				
	ไม่เปลี่ยน	ดีขึ้นเล็กน้อย	ดีขึ้นปานกลาง	ดีขึ้นมาก	ดีขึ้นมากที่สุด		ไม่เปลี่ยน	ดีขึ้นเล็กน้อย	ดีขึ้นปานกลาง	ดีขึ้นมาก	ดีขึ้นมากที่สุด
	0	+1	+2	+3	+4		0	+1	+2	+3	+4
	0%	1-25%	26-50%	51-75%	76-100%		0%	1-25%	26-50%	51-75%	76-100%
บวม											
แดง											
จุยลอก											
สะเก็ด											
	ไม่เปลี่ยนแปลง	แย่ลงเล็กน้อย	แย่ลงปานกลาง	แย่ลงมาก	แย่ลงมากที่สุด		ไม่เปลี่ยนแปลง	แย่ลงเล็กน้อย	แย่ลงปานกลาง	แย่ลงมาก	แย่ลงมากที่สุด
	0	-1	-2	-3	-4		0	-1	-2	-3	-4
สีผิวเข้มขึ้น											
เกิดผด											
เกิดสิว											

อาการผิดปกติอื่นๆ _____

Expert panel assessment: Laser treatment result

ผู้ประเมิน _____

การเปรียบเทียบผลการรักษาหลังทำเลเซอร์เทียบกับก่อนทำเลเซอร์

Subject No. _____

__day30 __day60

	แย่ลงมากที่สุด	แย่ลงมาก	แย่ลงปานกลาง	แย่ลงเล็กน้อย	ไม่เปลี่ยนแปลง	ดีขึ้นเล็กน้อย	ดีขึ้นปานกลาง	ดีขึ้นมาก	ดีขึ้นมากที่สุด
	-4	-3	-2	-1	0	+1	+2	+3	+4
	-76%-100%	-51%-75%	-26%-50%	-1%-25%	0%	+1%-25%	+26%-50%	+51%-75%	+76%100%
ใบหน้าด้านซ้าย									
หลุมสิว									
รูขุมขน									
ความเรียบเนียน									
ผลโดยรวม									
ใบหน้าด้านขวา									
หลุมสิว									
รูขุมขน									
ความเรียบเนียน									
ผลโดยรวม									

สิ่งตรวจพบอื่นๆ _____

APPENDIX C
QUESTIONAIRES

ชื่อ_____ No.___Date_____

แบบสอบถามอาการข้างเคียงหลังการรักษา OD1 OD3 OD5 OD7 OD14 OD30 OD60

โปรดทำเครื่องหมายในช่องที่ตรงกับอาการของท่านมากที่สุด

	ใบหน้าด้านขวา						ใบหน้าด้านซ้าย				
	ไม่มี	มีเล็กน้อย	มีปานกลาง	มีมาก	มีมากที่สุด		ไม่มี	มีเล็กน้อย	มีปานกลาง	มีมาก	มีมากที่สุด
	0	+1	+2	+3	+4		0	+1	+2	+3	+4
	0	+1-25%	+26-50%	+51-75%	+76-100%		0	+1-25%	+26-50%	+51-75%	+76-100%
ปวด											
แสบ											
คัน											
บวม											
แดง											
น้ำเหลือง											
ผิวแห้ง											
ผิวขุยสะเก็ดสีน้ำตาล											
หน้าออก											
อาการคัน											
สีผิวเข้มขึ้น											
การเกิดพื้นคล้ายสิว											
ผด											
ผิวหนังไวต่อสิ่งกระตุ้น											

อาการผิดปกติอื่นๆ (โปรดระบุ).....

APPENDIX D

DERMATOLOGY QUALITY OF LIFE INDEX (DQLI)

จุดประสงค์ของแบบสอบถามนี้ เพื่อประเมินว่า ผื่นผิวหนังทำให้เกิดปัญหากับคุณมากน้อยเพียงใดในช่วงหนึ่งสัปดาห์ที่ผ่านมา? **กรุณาตอบคำถามโดยทำเครื่องหมาย ✔ ลงในช่องทางขวามือ (ขอความกรุณาตอบคำถามทุกข้อ)**		
1. ช่วงสัปดาห์ที่ผ่านมา คุณมีอาการคัน, เจ็บ, ปวด, หรือปวดเสียว ที่ผิวหนังมากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	
2. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณรู้สึกอับอาย, ขาดความมั่นใจ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	
3. ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการออกจากบ้านไปจับจ่ายซื้อสินค้า, ดูแลบ้าน หรือดูแลสวน มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
4. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเลือกเสื้อผ้าที่จะสวมใส่ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
5. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเข้าสังคม หรือต่อกิจกรรมในยามว่าง มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
6. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลกระทบต่อการเล่นกีฬา การออกกำลังกายของคุณ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
7. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลทำให้คุณขาดงานหรือขาดเรียนหรือไม่	มี ☐ ไม่มี ☐	ไม่มีความเกี่ยวข้อง ☐
ถ้า "ไม่มี" ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้มีคุณมีปัญหาในการทำงาน หรือ การเรียน มากน้อยเพียงใด	ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	
8. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ ได้สร้างปัญหาให้กับคู่ครอง หรือญาติหรือเพื่อนสนิท มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
9. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการมีเพศสัมพันธ์ มากน้อยเพียงใด	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐
10. ช่วงสัปดาห์ที่ผ่านมา การรักษาผื่นผิวหนังก่อให้เกิดปัญหาแก่คุณ มากน้อยเพียงใด เช่น ทำให้มีการเปรอะเปื้อนในบ้าน, การรักษาทำให้เสียเวลา เป็นต้น	มาก ☐ ปานกลาง ☐ เล็กน้อย ☐ ไม่มีเลย ☐	ไม่มีความเกี่ยวข้อง ☐

APPENDIX E

THE ASSESSMENT OF SUNSCREEN KNOWLEDGE

ข้อมูลส่วนตัว					
1. **อายุ**	.....ปี.....เดือน				
2. **เพศ**	ชาย	หญิง			
3. **เชื้อชาติ**	ไทย	จีน	อื่น ๆ ระบุ.....		
4. **ระดับการศึกษา**	ประถมศึกษา	มัธยมศึกษา/ปวช	อนุปริญญา/ปวส		
	ปริญญาตรี	ปริญญาโท	สูงกว่าปริญญาโท		
5. **ระดับสีผิว**	น้ำตาลเข้ม/ดำ	น้ำตาล	น้ำตาลอ่อน/เนื้อ	ขาว/เหลือง	ขาว/ชมพู
6. **อาชีพ**	นักเรียน นักศึกษา	รับราชการ	รัฐวิสาหกิจ	พนักงานบริษัท	
	ธุรกิจส่วนตัว	แพทย์ พยาบาล	อื่น ๆ ระบุ.....		
7. **รายได้ต่อเดือน**	< 30,000	30,000-50,000	50,000-100,000	> 100,000	
ข้อมูลการเข้ารับการรักษา					
8. **ปัญหาสิ่งผิวหนังที่ทำให้ท่านมาทำเลเซอร์คือ (ตอบได้มากกว่า 1 ข้อ)**	ฝ้า	กระ	จุดด่างดำ	สิวอักเสบ	สิวผด
	สิว	รอยแดงสิว	หลุมสิว	ริ้วรอย	หย่อนคล้อย
	สิวอุดตัน	แผลเป็น	อื่น ๆ ระบุ.....		
ข้อมูลการทาเลเซอร์ (ตอบคำถามข้อนี้สำหรับผู้ที่เคยทาเลเซอร์มาแล้วในอดีต)					
9. **ท่านเคยทาเลเซอร์มาแล้วหรือไม่**	เคย (โปรดตอบคำถามข้อ 9-11)		ไม่เคย (โปรดข้ามไปตอบคำถามตั้งแต่ข้อ12)		
10. **จำนวนครั้งที่ท่านเคยทาเลเซอร์มาแล้ว**	1-3 ครั้ง	4-6 ครั้ง	7-9 ครั้ง	10 ครั้ง หรือมากกว่า	
11. **ท่านทราบชื่อ หรือชนิดเลเซอร์ หรือไม่**	ทราบ โปรดระบุ.....		ไม่ทราบ		
12. **ท่านมีอาการข้างเคียงหลังทาเลเซอร์หรือไม่**	มี (ได้แก่ รอยไหม้ รอยดำ รอยแดง ผิวหนังอักเสบ รอยแผลเป็น อื่น ๆ โปรดระบุ.....)				
	ไม่มี				
ข้อมูลพื้นฐานเกี่ยวกับผิวและการป้องกันแสงแดด					
13. **ท่านใช้เวลาอยู่กลางแดดในช่วงเวลา 10.00-16.00 น. เฉลี่ยเป็นเวลานานเท่าใด**	น้อยกว่า 30 นาที/วัน		30 นาที ถึง 1 ชั่วโมง/วัน		
	1-2 ชั่วโมง/วัน		มากกว่า 3 ชั่วโมง/วัน		
14. **ในช่วงระยะเวลา 12 เดือนที่ผ่านมา ท่านเคยมีปัญหาผิวไหม้แดด แดงอักเสบ กี่ครั้ง**	ไม่มีผิวไหม้แดดในช่วง 12 เดือน		1 ครั้งในช่วง 12 เดือน	2 ครั้งในช่วง 12 เดือน	
	3 ครั้งในช่วง 12 เดือน		4 ครั้งหรือมากกว่า ในช่วง 12 เดือน		
	ไม่เคย	นานๆ ครั้ง (ไม่เกิน 1 ครั้ง/สัปดาห์)	บางครั้ง (2-3 ครั้ง/สัปดาห์)	บ่อยครั้ง (4-6 ครั้ง/สัปดาห์)	ทุกวัน
15. **ทาครีมกันแดดก่อนออกแดด**					
16. **สวมหมวกปีกกว้าง ป้องกันแดด**					
17. **หลบแดดไปอยู่ในที่ร่ม**					
18. **กางร่มป้องกันแสงแดด**					
19. **สวมแว่นตากันแดด**					
20. **ท่านจะเลือกใส่เสื้อผ้าแบบใดเพื่อป้องกันแสงแดด**	ผ้าทอเนื้อแน่นใส่หลวม	ผ้าทอเนื้อแน่นใส่พอดีตัว		ผ้าทอเนื้อห่างใส่หลวม	
	ผ้าทอเนื้อห่างใส่พอดีตัว	ไม่ทราบ/ไม่แน่ใจ			
	หมวก cap	หมวกปีกกว้าง			

ท่านจะเลือกสวมหมวกแบบใดเพื่อป้องกันแสงแดด	หมวกผ้าคลุมคอ ไม่ทราบ/ไม่แน่ใจ		
22. ท่านจะเลือกครีมกันแดดที่มีค่าป้องกันแสงแดด แบบใด	UVA ไม่ทราบ/ไม่แน่ใจ	UVB	ทั้ง UVA, UVB
23. ถ้าท่านจะใช้ครีมกันแดด ท่านจะเลือกครีมกันแดดที่มีค่า SPF เท่าใด	SPF < 30 ไม่ทราบ/ไม่แน่ใจ	SPF 30-50	SPF > 50
24. ถ้าท่านจะใช้ครีมกันแดด ท่านจะเลือกครีมกันแดดที่มีค่า PA เท่าใด	PA + ไม่ทราบ/ไม่แน่ใจ	PA ++	PA +++
25. ถ้าท่านจะใช้ครีมกันแดด ท่านจะใช้ครีมกันแดดปริมาณเท่าใดสำหรับใบหน้า	1 เม็ดถั่วเขียว 2 ข้อนิ้วมือ	ครึ่งข้อนิ้วมือ ไม่ทราบ/ไม่แน่ใจ	1 ข้อนิ้วมือ
26. ถ้าท่านจะใช้ครีมกันแดด ท่านจะทาครีมกันแดดเมื่อใด	ทาเฉพาะวันที่อยู่ในบ้าน ทาทุกวันไม่ว่าอยู่ใน/นอกบ้าน	ทาเฉพาะวันที่ออกนอกบ้าน	
27. ถ้าท่านจะใช้ครีมกันแดด ท่านจะทาครีมกันแดดก่อนออกไปอยู่กลางแดดอย่างไร	ทาทันทีก่อนออกแดด 20-30 นาทีก่อนออกแดด	5-10 นาทีก่อนออกแดด ไม่ทราบ/ไม่แน่ใจ	
28. ถ้าท่านจะใช้ครีมกันแดด เมื่อทาและออกแดดไปแล้ว ท่านจะทาครีมกันแดดซ้ำอีกหรือไม่	ไม่ทาซ้ำเลย ทาซ้ำทุก 2 ชั่วโมงเมื่ออยู่กลางแดด	ทาซ้ำอย่างน้อย 1 ครั้งเมื่ออยู่กลางแดด ทาซ้ำเมื่อรู้สึกว่าผิวต้องการ	
29. ท่านเลือกที่จะป้องกันแสงแดดด้วยเหตุผลใด (ตอบได้มากกว่า 1 ข้อ)	ป้องกัน ฝิวไหม้คล้ำ ป้องกันริ้วรอยก่อนวัย	ป้องกันฝ้า กระ ป้องกันมะเร็งที่ผิวหนัง	

ข้อมูลเรื่องการป้องกันอาการข้างเคียงหลังจากการทำเลเซอร์			
	ใช่/ทราบ	ไม่ใช่/ไม่ทราบ	ไม่แน่ใจ
30. ในอดีต หลังการทำเลเซอร์ ท่านได้ทาครีมกันแดด หรือไม่			
31. ท่านทาครีมกันแดดอย่างต่อเนื่องเป็นเวลา 4-6 สัปดาห์ ก่อนการทำเลเซอร์ หรือไม่			
32. ท่านได้ทายาลดอาการอักเสบบนผิวหนัง หลังทำเลเซอร์หรือไม่			
33. ท่านได้ป้องกันแสงแดด เช่น สวมหมวก กางร่ม ในบริเวณที่ทำเลเซอร์ไปแล้วหรือไม่			
34. ท่านได้ทาครีมกันแดดในบริเวณที่ทำเลเซอร์ไปแล้วหรือไม่			
35. ถ้าเลือกที่จะใช้ครีมกันแดด ท่านจะเริ่มทาครีมกันแดดเมื่อใด	ทันทีหลังทำเลเซอร์ 2-3 วันหลังทำเลเซอร์	วันรุ่งขึ้นหลังทำเลเซอร์ หลังแผลจากการทำเลเซอร์หายไปแล้ว	

APPENDIX F

ACCEPTANCE LETTER FOR PROCEEDING

The JSPS-NRCT Follow-Up Seminar 2017 and 33rd International Annual Meeting in Pharmaceutical Sciences (JSPS-NRCT 2017 and IAMPS33)
Faculty of Pharmaceutical Sciences, Chulalongkorn University
254 Phayathai Road, Patumwan, Bangkok 10330 THAILAND
Tel: +66 2218 8261 Fax: +66 2255 8227

Date: 15 March 2017

Proceeding manuscript:
Efficacy and safety of moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese versus 0.02% triamcinolone acetonide cream in decreasing adverse reaction and downtime after ablative fractional carbon dioxide laser resurfacing

Authors:
Aphinut Srituravanit, Phubodin Vongtaranavuth, Suparuj Lueangarun

Dear Mr. Aphinut Srituravanit,

We are pleased to inform you that your proceeding manuscript has been accepted for presentation in the JSPS-NRCT Follow-Up Seminar 2017 and 33rd International Annual Meeting in Pharmaceutical Sciences (JSPS-NRCT 2017 AND IAMPS 33), which is held on 2-3 March 2017 at The Berkeley Hotel Pratunam, Bangkok, Thailand. Your proceeding manuscript will be published The Thai Journal of Pharmaceutical Sciences (TJPS), 2017, vol.41 (Supplement Issue), page 37-40

Yours truly,

Pornchai R.

Assoc. Prof. Pornchai Rojsitthisak, Ph.D.

Chair of Scientific Program Committee

APPENDIX G
FULL MANUSCRIPT FOR PROCEEDING

TJPS Vol.41 (Supplement Issue) 2017

Thai Journal of Pharmaceutical Sciences (TJPS)
The JSPS-NRCT Follow-Up Seminar 2017 and
33rd International Annual Meeting in Pharmaceutical Sciences

Efficacy and safety of moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese versus 0.02% triamcinolone acetonide cream in decreasing adverse reaction and downtime after ablative fractional carbon dioxide laser resurfacing

Aphinut Srituravanit[1], Phubodin Vongtaranavuth[1,2], Suparuj Lueangarun[1,*]

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Keywords: Panthenol, Madecassoside, Copper-Zinc-Manganese, Fractional ablative laser, Wound healing

Introduction

Fractional carbon dioxide ($FrCO_2$) laser is one of the ablative fractional laser resurfacing (AFR) based on the principle of fractional photothermolysis (FP), by which the 10,600-nm wavelength of the carbon dioxide (CO_2) laser is combined with an FP system. The laser ablates epidermis and heats dermal tissue in the so called microscopic treatment zones (MTZs), consisting of sharply columnar tissue denaturation of about 100 µm diameter surrounded by viable tissue.[1] However, the downtime following this laser procedure is often unavoidable despite being an effective tool for atrophic acne scar treatment.[2]. The downtime includes white frosting, likely to last for 5 to 10 minutes immediately after laser irradiation, followed by moderate to marked erythema and edema, usually persisting for 24 hours. Normally, superficial crusting occurs and re-epithelialization is completed within 5 to 7 days, depending on density and energy of the laser. Whilst, post-inflammatory hyperpigmentation (PIH) can be observed after the slough-off crusts, normally around 1 or 2 weeks following the procedure.[2]

In a recent study, short-term application of postoperative topical steroid could decrease the risk of this downtime after AFR, yet unfavourably disturbed the wound healing process and possibly increased the risk of postoperative skin infection or acneiform eruption as well.[3] In this study, 2/40 subjects with topical steroid treatment for 2 days post-operatively developed acneiform eruption. Thus, we aimed to investigate an alternative treatment modality to improve postoperative $FrCO_2$ laser downtime so that steroid-treated adverse effects could be avoided by using non-steroidal anti-inflammatory agents.

Alternatively, the moisturizer containing 5% Panthenol, Madecassoside, and Copper-Zinc-Manganese (Cicaplast Baume B5, La Roche-Posay, France) is a multi-purpose soothing balm for normal and sensitive skin irritations. With 3 active-ingredients including Dexpanthenol, Madecassoside, and Copper-Zinc-Manganese, this product can yield various positive effects in wound healing process. Dexpanthenol (an active form of panthenol) is the stable alcoholic analoque of pantothenic acid (vitamin B5), known to improve skin barrier by decreasing transepidermal water loss (TEWL), maintaining skin softness, activating fibroblast proliferation, and providing anti-inflammatory effect.[4] Madecassoside, the extract from Centella asiatica, can induce collagen expression, modulate inflammatory mediators, prevent aging, and inhibit proliferation of keloid fibroblast.[5, 6] Copper-Zinc-Manganese possesses healing properties and improves skin functions by stimulating the keratinocyte proliferation and fibroblasts migration in the skin.[7]

Moreover, this moisturizer containing anti-inflammatory ingredients has also been identified for its treatment efficacy in various skin conditions, such as atopic dermatitis and irritative dermatitis, and is also well-tolerated for most of the patients.[8, 9]Postoperatively, the use of this cream following the $FrCO_2$ laser could be a novel treatment modality to decrease the post-ablative laser downtime by using non-steroidal moisturizer containing anti-inflammatory ingredients.

Methods

Patients: Twenty subjects aged ≥18 years with atrophic acne scars on both cheeks for at least 6 months were recruited to this split-face, double-blind, randomized controlled trial. Given verbal and written information, all subjects signed the inform consent forms before enrollment. Exclusion criteria were subjects who were pregnant or lactating, received isotretinoin, or underwent invasive facial procedures within the preceding 3 months, as well as those with skin infections or photosensitive skin, and concomitant treatment to the involved skin areas or a propensity for keloid scarring.

Treatment: Preoperatively, lidocaine 2.5% and prilocaine 2.5% cream (Liprikaine; a eutectic mixture of local anaesthetic, T.Man Pharmaceutical Co., Ltd, Thailand) was applied under occlusion for 40 minutes before performing $FrCO_2$ laser (eCO2; Lutronic Co., Ltd, South Korea) on both cheeks by a single physician following these parameters of static mode: 120 µm beam size, 30 w peak power, 60 mj pulse energy, 1 mm ablation depth, with 2 passes of 100 spots/cm2 density and less than 15% coverage. Besides, no concurrent use of epidermal cooling device was performed during the procedure. No postoperative analgesic treatment was required beyond the application of ice compresses for approximately 15–20 min. No prophylactic antibiotics or antivirals were given to any patients.

Postoperative care: Immediately after the laser irradiation, all subjects were taken high-resolution camera images of their faces in 5 positions, with facial scanning by Antera (Antera 3D®; Miravex Co., Ltd, Dublin, Republic of Ireland) device before allowed for ice compression. Two sides of each patient's face were randomly treated with 2 different post-treatment agents; one side of the face with the experimental cream (moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese) twice daily for 7 days, while the other side with 0.02%TA cream twice daily for 7 days. All subjects must use 2 separated cotton-buds for applying each cream to avoid contamination. Moreover, they were instructed to wear a broad-spectrum sunscreen with a sun protection factor of 40, avoid sun exposure or use of any topical preparations on the face during the period of study.

Evaluation: All subjects were evaluated on the experimental day (before and immediately after laser irradiation) and additional 4 follow-up visits including day 3, day 5, day 7, and day 14 after irradiation. The evaluation included questionnaires, facial examination, downtime and side effects reported by subjects, high resolution camera imaging, and facial scanning by the Antera device. The pain related to laser procedure was also recorded as the 0-10 pain score, immediately after the laser irradiation.

The facial examination included overall facial skin, erythema, scaling, crusting, dyspigmentation, PIH, skin texture, pore, acne scar, and other side effects. The questionnaires were also completed for downtime and side effects observed by the subjects. Meanwhile, the photographic images were obtained by using a digital camera (Canon PowerShot G1 X Mark II Digital Camera; Canon Marketing Co., Ltd, Thailand) Canon PowerShot G1X with the same camera settings, lighting, and positioning on every visit. The positioning was comprised of 5 positions; frontal, 45 degree left-lateral and right-lateral, and 90 degree left-lateral and right-lateral. Whereas, the Antera facial scanning was obtained in a bid to evaluate the following parameters; haemoglobin (erythema), melanin, elevations (crusting and scaling), pore, depressions (atrophic scars), skin colour, and skin texture.

Results

Demographic data

Twenty subjects (12 males, 8 females) with the mean±SD age of 37.55±9.41 years (range 26-46) and skin phototype IV were enrolled and completed the study.

Efficacies evaluation using biometric facial scan (Antera 3D)

In the experimental cream treated group, haemoglobin index reached its peak (1.91±0.17) at day 3 before significantly decreased (1.64±0.14) at day 14 ($p<0.001$). Melanin index reached its peak (0.57±0.06) at day 3 and significantly decreased (0.56±0.07) at day 14 ($p < 0.05$). Meanwhile, scale reached its peak (9.46±4.88) immediately after laser treatment, then significantly improved (6.80±4.27) at day 14 ($p<0.001$)

Table 1 Improvement of $FrCO_2$ laser's side effects on the side treated with experimental cream

	Before	After	Day 3	Day 5	Day 7	Day 14	P-value*
Atrophic scar	11.26±8.08	12.53±8.89	10.46±7.66	11.19±8.48	11.99±9.62	11.93±8.57	0.164
Hemoglobin	1.56±0.17	1.82±0.13	1.91±0.17	1.72±0.16	1.65±0.15	1.64±0.14	<0.001
Melanin	0.56±0.07	0.56±0.05	0.57±0.06	0.56±0.06	0.56±0.06	0.56±0.07	0.019
Pores	5.91±3.52	9.18±4.65	7.29±4.01	6.12±3.78	6.17±3.89	6.47±4.17	<0.001
scale	5.96±3.59	9.46±4.88	7.43±4.00	6.24±3.76	5.97±4.12	6.80±4.27	<0.001
Texture	25.85±1.84	28.54±12.22	25.34±10.19	26.67±12.30	27.08±13.19	26.94±11.65	0.061

*Friedman Test, Post Hoc: Wilcoxon Signed Ranks Test (P-value<0.003)
Whilst, in the 0.02% TA cream treated group, haemoglobin index reached its peak of 1.89±0.18 at day 3, then significantly decreased (1.60±0.15) at day 14 (p<0.001). Melanin index reached its peak of 0.58±0.05 at day 3 and significantly decreased (0.56±0.07) at day 14 (p < 0.001). Scale index, reached its peak of 8.82±5.52 immediately after laser treatment before significantly improved (5.81±4.11) at day 14 (p<0.001) (Table 2).

Table 2 Improvement of $FrCO_2$ laser's side effect on the side treated with the 0.02% TA cream

	Before	After	Day 3	Day 5	Day 7	Day 14	P-value*
Atrophic scar	11.75±8.52	11.77±9.59	9.94±7.02	11.07±8.10	10.69±8.21	11.23±8.40	0.177
Hemoglobin	1.53±0.13	1.83±0.15	1.89±0.18	1.67±0.16	1.55±0.31	1.60±0.15	<0.001
Melanin	0.57±0.07	0.56±0.05	0.58±0.05	0.56±0.05	0.56±0.06	0.56±0.07	<0.001
Pores	6.13±4.06	8.55±5.24	6.53±3.38	5.99±3.85	5.67±3.97	5.87±3.91	<0.001
Scale	6.13±3.12	8.82±5.52	6.72±3.33	6.08±3.93	5.72±4.18	5.81±4.11	<0.001
Texture	26.43±11.53	27.58±13.19	24.55±9.09	25.55±10.98	25.07±11.31	25.93±11.16	0.085

*Friedman Test, Post Hoc: Wilcoxon Signed Ranks Test (P-value<0.003)

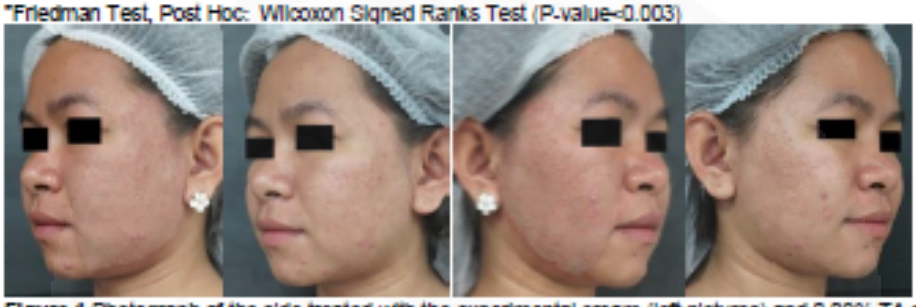

Figure 1 Photograph of the side treated with the experimental cream (left pictures) and 0.02% TA cream (right pictures) immediately after laser treatment and day 14

Interestingly, there was no significant difference in haemoglobin index, melanin index, and scale index between the moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese and the 0.02% TA cream at any time point (p>0.05). Moreover, no significant difference of skin texture, pores, and atrophic scar volume was observed between the experimental cream and the 0.02% TA cream from baseline to day 14.
The wound healing and downtime evaluated by subjects: There was no significant difference in the improvement of redness, swelling, and burning feeling between the experimental cream and the 0.02% TA cream from baseline to day 14.
Adverse effects: 1 (5.0%) of 20 subjects postoperatively developed acneiform eruption on both sides of the face at the day 3. Additionally, 1 subject (5.0%) complained of mild erythema and tingling feeling on the face of both sides after washing, but not observed by the investigator. While, the pain score after treatment ranged from 4 to 8 with the mean score of 6.95.

Discussion

In our study, the experimental cream containing anti-inflammatory ingredients yielded the efficacy to decrease downtime after $FrCO_2$ laser irradiation, including erythema, melanin, scale, redness, swelling, and burning feeling, comparable to the 0.02% TA cream. These improved wound healing efficacies and decreased downtime after laser treatment resulted from the active ingredients. Typically, panthenol itself maintains an anti-inflammatory effect crucial to prevent PIH caused by the increasing of melanin distribution and melanin production from various released inflammatory mediators, such as prostaglandin E2, D2, leukotriene C4, D4, and thromboxane-2.[10] Additionally, panthenol also improves skin barrier by decreasing TEWL and maintaining skin softness[4], consistent with the improved scaling and crusting in our study. In the meantime, madecassoside modulates the inflammatory mediators and stimulates collagen expression.[5, 6] Finally, copper-zinc-manganese complexes are the trace elements for skin function improvement by regulating keratinocyte proliferation[7] related to the wound healing process and scale-crust improvement in this study.

A recent study conducted by Manuskiatti et al. in 2015 revealed that short-term application of high potency topical steroid 0.05% Clobetasol propionate for 2 days after treatment could decrease the risk of PIH and other downtimes following AFR.[3] However, there were 2/40 subjects developing acneiform eruption on the treated side with high potency steroid. As a consequence, we used low potency topical steroid and moisturizer with anti-inflammatory ingredients to achieve the efficacious results for downtime improvement after AFR and prevention of adverse effects from high potency steroid. However, there was one subject with acneiform eruption development on both sides of the face at the day 3 after laser treatment in our study, possibly the side effect of AFR. Besides, the experimental cream was well tolerated by all subjects.

Hence, the applying of non-steroidal anti-inflammatory moisturizer in our study could be a novel treatment modality to decrease post-ablative downtime and to avoid adverse effects from the steroid, leading to wound healing process improvement. Nevertheless, further study on the long term effect of this product is recommended due to some limitations including small sample size, short period of follow up, and only the study in Asian population with skin phototype IV. Thus, more sample size, more skin color variation, and a longer study period are suggested to obtain more accurate treatment results of this non-steroidal anti-inflammatory moisturizer to improve the wound healing process and decrease the downtime after AFR.

Conclusion

Moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese yielded a comparable efficacy to 0.02% TA cream in decreasing adverse reactions and downtime after $FrCO_2$ laser irradiation. Alternatively, this moisturizer could be a novel treatment modality for the post-ablative laser downtime with the use of non-steroidal anti-inflammatory agents to avoid high potency steroid adverse effects and improve wound healing process.

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APPENDIX H
CERTIFICATE OF ETHICAL APPROVAL

Certificate of Approval

The Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine)

95 Moo 8, Paholyotin Road, Auphur Klongluang, Pathumthani. Thailand 12120,

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Number of COA	**056/2017**
Title of Project	Triamcinolone acetonide :Efficacy and Safety of Moisturizer Containing 5% Panthenol, Madecassoside, and Copper - Zinc - Manganese vs 0.02% Triamcinolone acetonide in improving Wound Healing after Ablative Fractional Carbon Dioxide Laser Resurfacing : A Split Face, Double-blind, Randomized, Controlled trials
Project No	MTU-EC-OO-2-119/59
Principal Investigator	Suparuj Lueangarun, M.D Phubodin Vongtaranavuth, M.D Aphinut Srituravanit
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Document Reviewed

1. Protocol Revise No 3: date March 4 , 2017.
2. Information Sheet Revise No 3: date March 4 , 2017.
3. Consent Form Revise No 3: date March 4 , 2017.
4. Case Record Form Revise No 3: date March 4 , 2017.
5. Advertising boards Revise No 3: date March 4 , 2017.

The Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine) is in full compliance with international such as Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Practice (ICH-GCP)

This document is a record of review and approval / acceptance of a clinical study protocol. The Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine) has approved the above study and the following documents for use in the study at the Ethics Committee meeting on August 9, 2016. (15/2016)

Approval period 1 year.

Progress report deadline : March 19, 2018

Signed: .....

(Assistant Professor Sumalee Kondo)

Assistant Secretary of the Human Research Ethics Committee of Thammasat University No.I

(Faculty of Medicine)

Signed:.....

(Associate Professor Waipoj Chanvimalueng (M.D.))

Chairman of the Human Research Ethics Committee of Thammasat University No.I

(Faculty of Medicine)

Date of Approval **:March 20, 2017**

Date of Expire **:March 19, 2018**

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