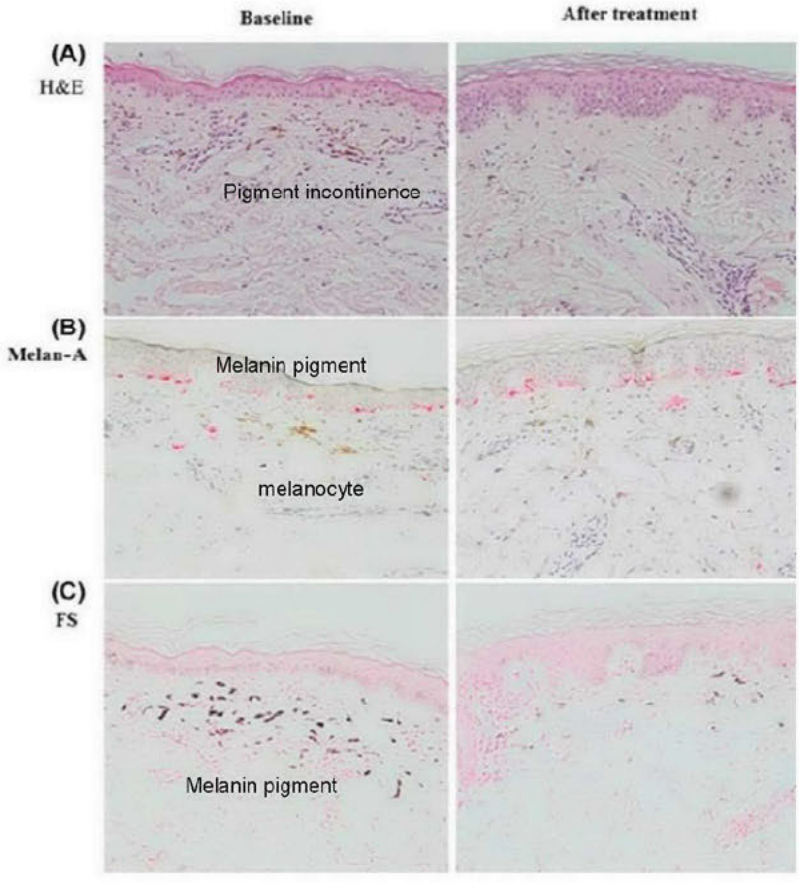
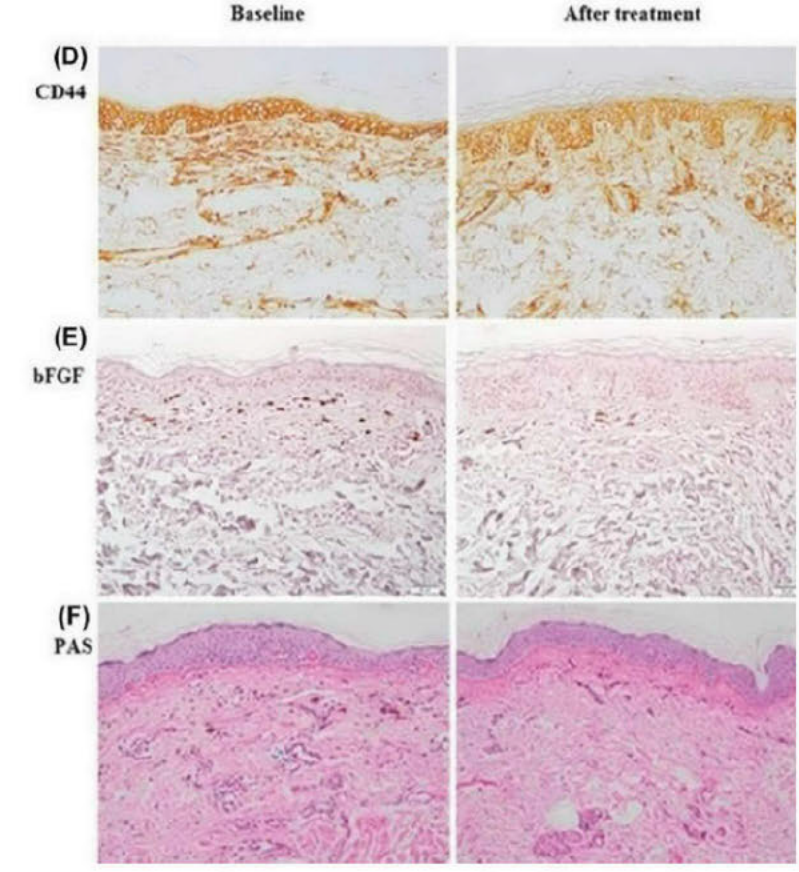
Pulsed Wave: Pigmented Lesion



- Histopathologic evaluation revealed that mild vacuolar alteration of the basal layer and pigment incontinence in the upper dermis were mainly found before treatment.
- Moderate perivascular inflammatory infiltration and proliferation of small blood vessels were also observed.
- 4 weeks after the final treatment, the amount of melanin pigment in the epidermis and dermis was reduced.
- The proliferation of melanophages and blood vessel in the dermis was reduced. Compared with the pretreatment state.

*Melan-A : to visualize melanocytes
*Fontana silver (FS) : to visualize melanin pigment



(D) CD44 was decreased in the epidermis and dermis.
(E) Basic fibroblast growth factor (bFGF) was decreased in the dermis after treatment.
(F) Basement membrane thickening was revealed 3 days after treatment.

*CD44 : a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration
*bFGF : a growth factor signaling protein involved in the proliferation and differentiation of numerous cell types and modul
*Periodic acid-Schiff (PAS) : to detect glycogen, and mucosubstances such as glycoproteins, glycolipids and mucins in tissues

VIOL-00000233
Ex. 2044-018
CX-2855C.18

Pulsed Wave: Pigmented Lesion



Senescent fibroblasts in melasma pathophysiology SCI(E) SCOPUS

By Misun Kim, So Min Kim, Soohyun Kwon, Tae Jun Park, and Hee Young Kang

Experimental Dermatology, 2019, 28(6), 719-722:
http://doi.org/10.1111/exd.13814

Methods

- To investigate whether melasma includes senescent cells, lesional and perilesional normal skin from 38 women melasma patients was assessed using a cell senescence marker, $p16^{INK4A}$.
- To further investigate the impact of senescent fibroblasts, a bipolar pulsed-type RF (SYLFIRM; ViOL) treatment were performed to 3 patients.
  - Biopsy Participants: mean age 45, Fitzpatrick skin type III-IV
  - Treatment Participants: 32-45 years old, Fitzpatrick skin type III-IV
  - Treatment: 1.5mm, level 2 for 5 sessions every 2 weeks

Results

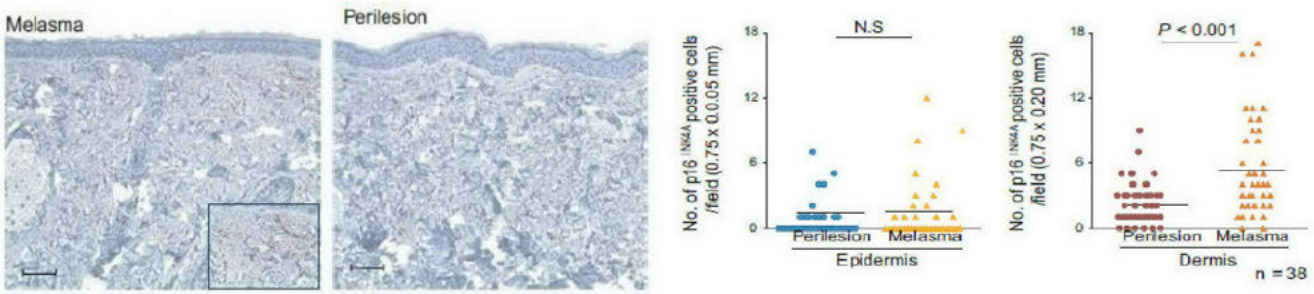
- The lesional dermal skin had more $p16^{INK4A}$-positive cells than perilesional skin.
- The RF therapy decreased the number of senescent cells with increased expression of procollagen-1, which were associated with reduced epidermal pigmentation.

VIOL-00000234

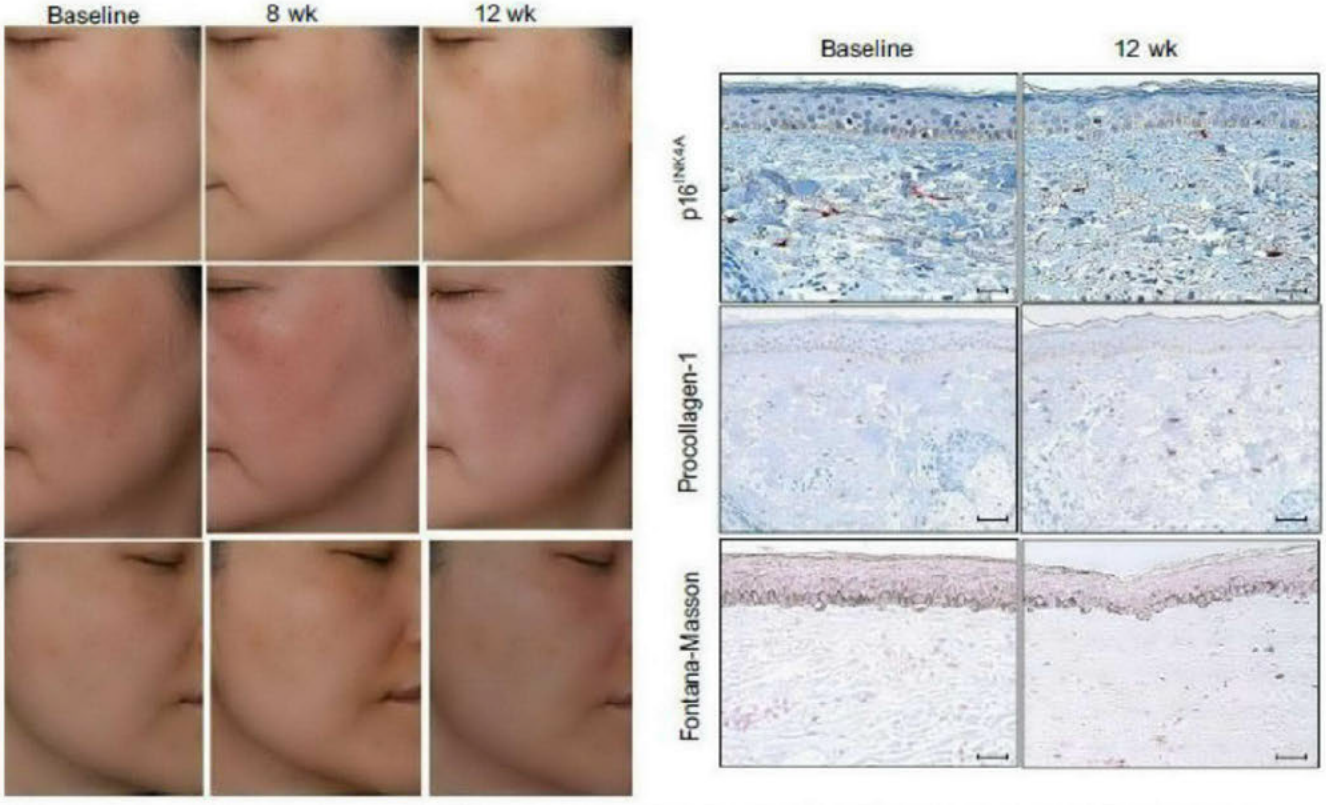
Ex. 2044-019

CX-2855C.19

Pulsed Wave: Pigmented Lesion



The number of p16^{INK4A}-positive cells was significantly higher in the dermis of lesional skin than in that of perilesional skin.
Most p16^{INK4A}-positive cells were observed in the superficial dermis near the epidermal-dermal junction, not in the deep dermis, suggesting the influence of UV irradiation on cellular senescence.



All subjects showed clinical improvement after RF treatment compared with baseline. The L*(lightens) value increased from the baseline.
Histologic analysis revealed that the RF treatment showed a reduction in p16^{INK4A}-positive cells and appeared to reverse the senescence-dependent decrease in collagen response, that is, there was an increase in the density of procollagen-1 after RF treatment.
These changes were associated with decreased pigmentation in the epidermis, that is, Fontana-Masson staining demonstrated a marked decrease in pigmentation of lesional skin compared with baseline values.

*p16^{INK4A}: a cell senescent marker
*Procollagen-1: a precursor of collagen
*Fontana-Masson stain: to identify melanin in tissues

[redacted]

VIOL-00000235
Ex. 2044-020
CX-2855C.20

Pulsed Wave: Pigmented Lesion



Senescent fibroblasts drive ageing pigmentation: A potential therapeutic target for senile lentigo

By Jung Eun Yoon, Yeongeun Kim, Soohyun Kwon, Misun Kim, Young Hwa Kim, Jang-Hee Kim, Tae Jun Park, and Hee Young Kang

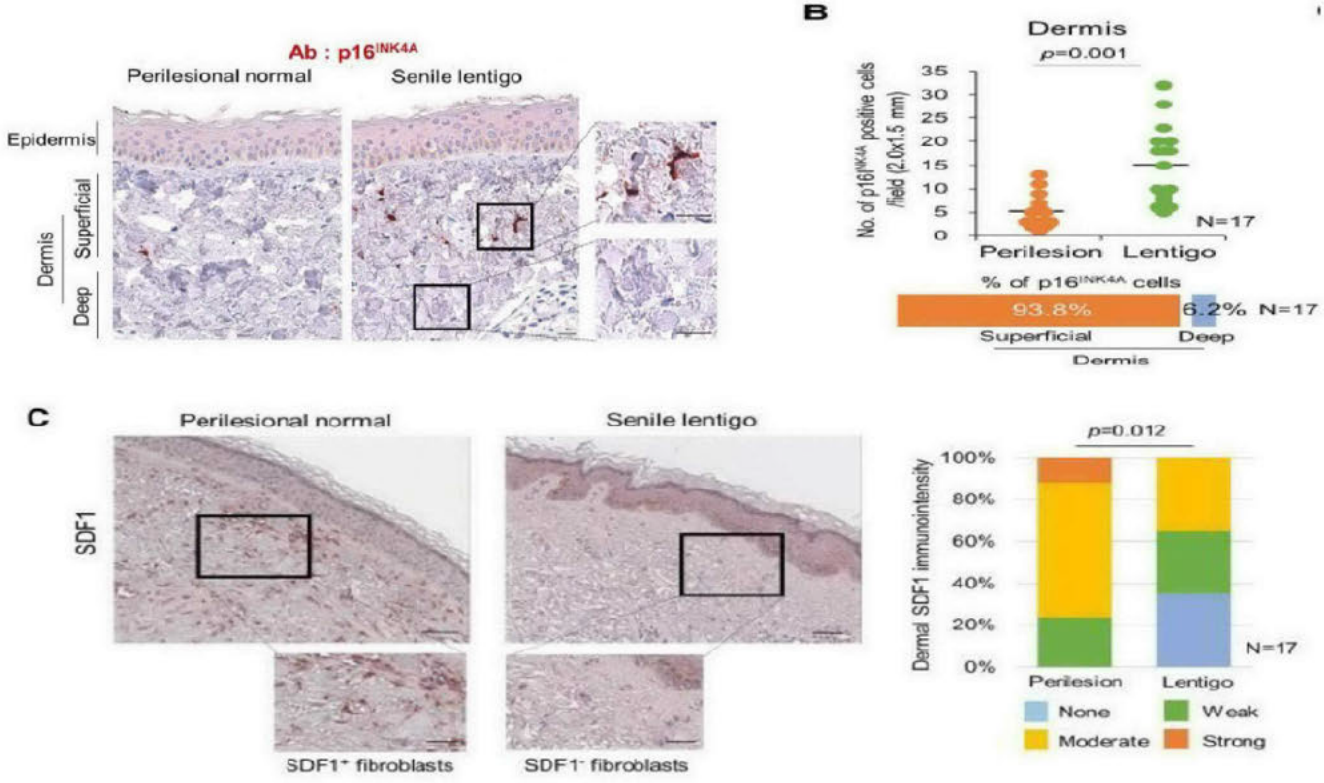
Theranostics, 2018, 8(17), 4620-4632:
https://doi.org/10.7150/thno.26975

Methods

- Biopsies obtained from senile lentigo and perilesional normal skin of 17 volunteers, were assayed for a marker of cellular senescence, $p16^{INK4A}$.
- To determine the secretory phenotypes of senescent fibroblasts, microarray, RNA sequencing and methylation array analyses were performed in senile lentigo and senescent fibroblasts.
- To further investigate the impact of senescent cells on ageing-related pigmentation, an intervention that targeted senescent cells using RF microneedling (SYLFIRM; ViOL) treatment were performed with level 6, weekly treatments for 6 weeks.

Results

- Aged pigmented skin contains an increasing proportion of senescent fibroblasts.
- Cells with phenotype switching exhibited a loss of SDF1, which stimulates the melanogenic process and thereby contributes to ageing pigmentation.



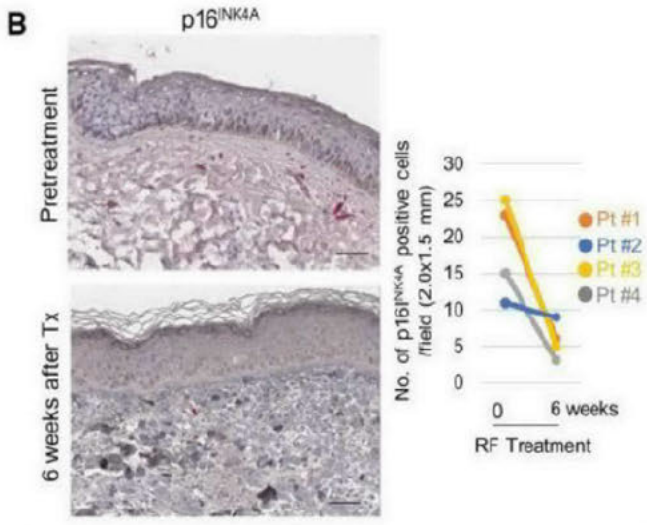
*SDF1 : Stromal derived factor-1, C-X-C motif chemokine ligand 12 (CXCL12), a widely expressed constitutive chemokine that regulates tissue homeostasis and inflammatory responses

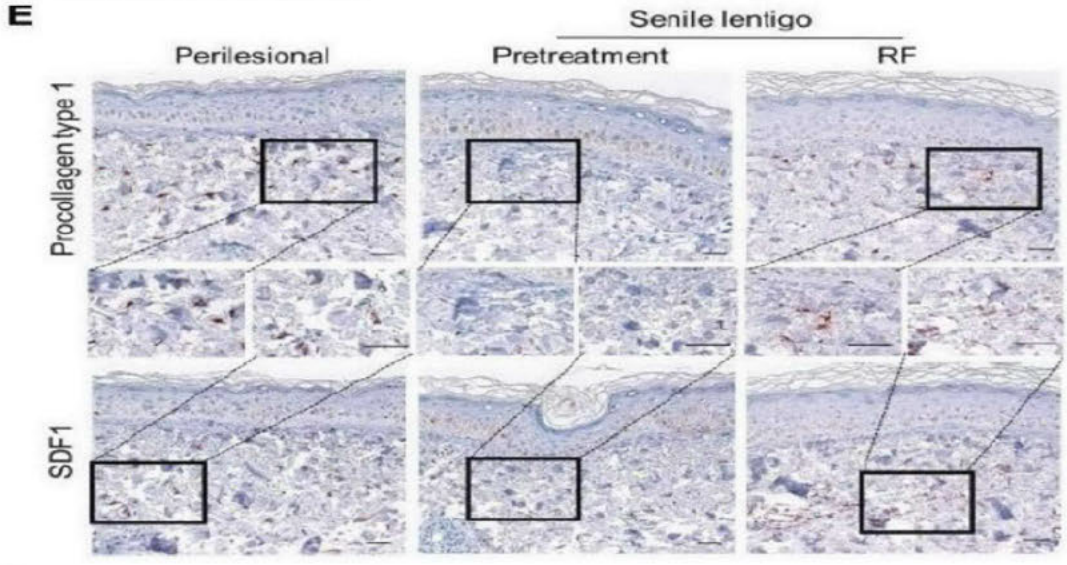
VIOL-00000236

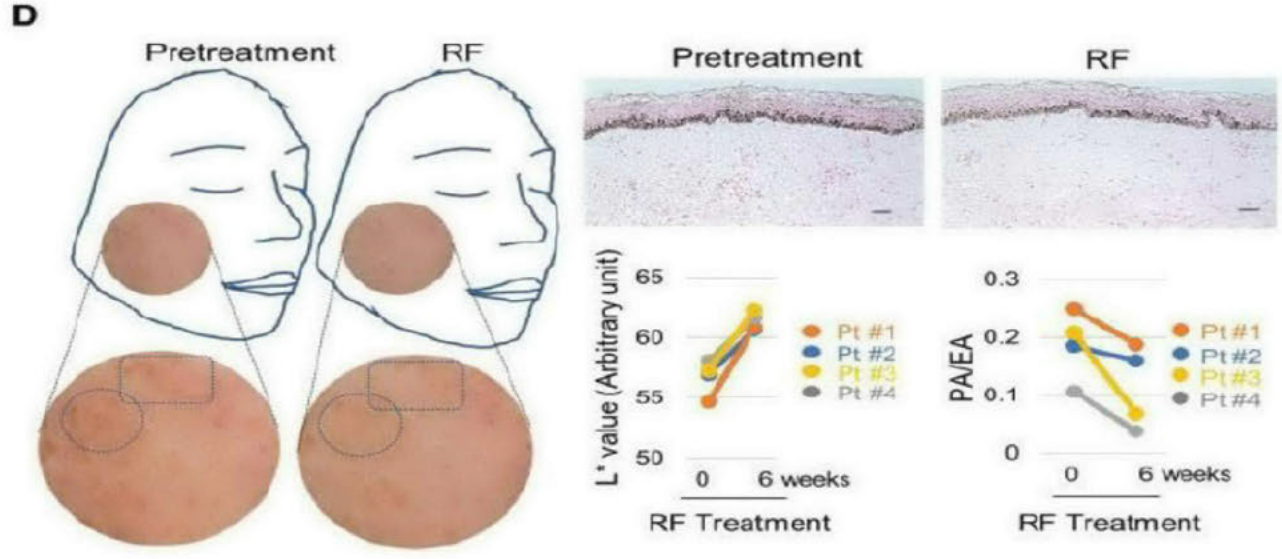
Ex. 2044-021

CX-2855C.21

Pulsed Wave: Pigmented Lesion







*p16INK4A : a cell senescent marker

*SDF1 : Stromal derived factor-1, C-X-C motif chemokine ligand 12 (CXCL12), a widely expressed constitutive chemokine that regulates tissue homeostasis and inflammatory responses

VIOL-00000237

Ex. 2044-022

CX-2855C.22

Pulsed Wave: Pigmented Lesion



Therapeutic Efficacy and Safety of Invasive Pulsed-Type Bipolar Alternating Current Radiofrequency on Melasma and Rebound Hyperpigmentation

By Hyoung Moon Kim, and Min Ji Lee

Medical Lasers, 2017, 6(1), 17-23:
http://doi.org/10.25289/ML.2017.6.1.17

Methods

- Clinical improvement in the appearances of melasma and rebound hyperpigmentation (RH) was analyzed in 142 Korean patients who undergone invasive pulsed-type bipolar radiofrequency (IBPRF) (SYLFIRM; ViOL) treatment with or without other methods.
  - 4 men and 138 women, a mean age of 37.3±11 years, 15 with melasma for < 1 year, 64 for 1-5 years, 53 for < 5years, 10 for > 10 years
  - Treatment Plan:
    - 112 patients received IBPRF alone
    - 22 patients received a combination of IBPRF plus a Q-switched Nd:YAG laser
    - 5 patients received IBPRF plus intralesional tranexamic acid injection
    - 3 patients received IBPRF plus bleaching cream
  - Treatment:
    - IBPRF: 1.5mm along the face, 1.0mm on forehead, level 2, 1pass
    - Q-switched Nd:YAG laser: 1064nm, 5-10ns, 7mm, 1.0-1.2J/cm², 2,000-2,500 shots on the entire face
    - 5-10 treatment sessions at 2-3 week intervals

Results

- Patients reported subjective satisfaction with the appearance of their melasma lesions after seven to eight treatment sessions.
- No significant complications, particularly RF or mottled hypopigmentation, were recorded.



(A) Baseline
(B) 1 month after 10 sessions of combined IBPRF monotherapy



(A) Baseline
(B) 1 month after 6 sessions of combined IBPRF and laser tonin g

Pulsed Wave: Pigmented Lesion



Successful Treatment of Refractory Melasma Using Invasive Micro-Pulsed Electric Signal Device
By Moon Choi, Seohee Choi, Jin-Soo Kang, and Sung Bin Cho
Medical Lasers, 2015, 4(1), 39-44:
http://doi.org/10.25289/ML.2015.4.1.39

Methods

- 5 female patients with refractory facial melasma, were treated with invasive micro-pulsed electric signal device (IMPES) (SYLFIRM; ViOL) added to their baseline of low-fluence Q-switched Nd:YAG laser (LFQSNY) / topical lightening agents (TLA) treatment.
  - Patients: Fitzpatrick skin types III-IV, aged between 42-53 years, mean 48 years
  - LFQSNY: 8mm, 1.89J/cm², 10hz, <10% overlap
  - IMPES: 1.2-1.7mm, level 3-5, single pass, <10% overlap
  - 4-7 treatments at 1-week intervals

Results

- At the last treatment, assessments showed greater than 50% clinical improvement in melasma in all 5 patients.
- No recurrence was reported during the follow-up at 8 weeks.
- Addition of IMPES to LFQSNY/TLA is a safe and effective treatment for refractory melasma.



(A) Baseline (B) 1 week after the last treatment *received additional procedure for facial seborrheic keratosis removal prior to IMPES treatment



(A) Baseline (B) 1 week after the last treatment



(A) Baseline (B) 1 week after the last treatment

VIOL-00000239
Ex. 2044-024
CX-2855C.24

Pulsed Wave: Vascular Lesion



Therapeutic effects of a new invasive pulsed-type bipolar radiofrequency for facial erythema associated with acne vulgaris and rosacea SCOPUS

By You Jin Jung, Young Suck Ro, Hwa Jung Ryu, and Jeong Eun Kim

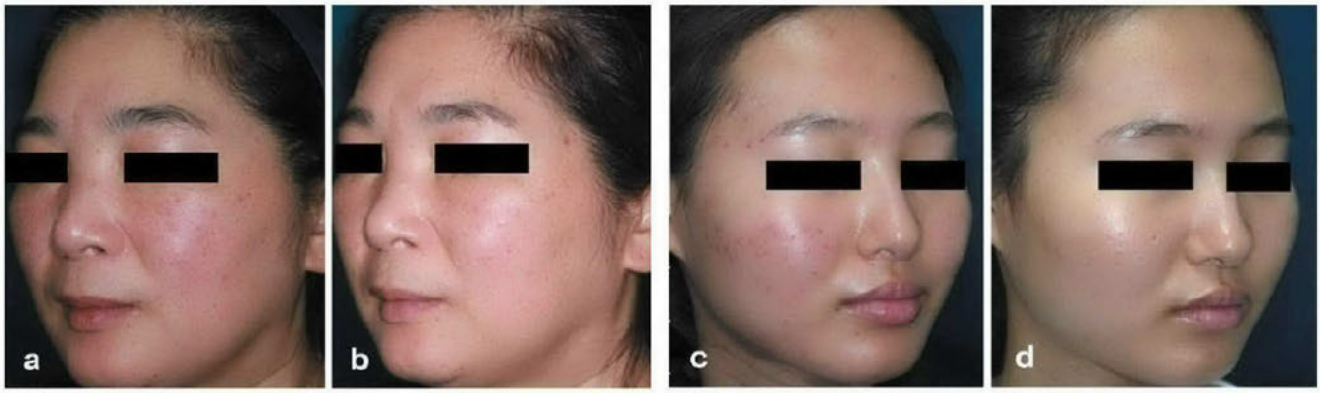
Journal of Cosmetic and Laser Therapy, 2020, 22(4-5), 205-209: http://doi.org/10.1080/14764172.2021.1880599

Methods

- 31 Korean patients with facial erythema from rosacea or acne vulgaris, underwent an invasive short pulsed-type bipolar radiofrequency (IPBRF) (SYLFIRM; ViOL) treatment.
  - Patients: 26 females and 5 males, mean age 30.9 years, range 14-51, Fitzpatrick skin type III-IV
  - IPBRF: level 4-6, 1.5mm on face, 1.0mm on forehead, 2-3passes, with <10% overlap for 2-5 treatment sessions at 2-week intervals

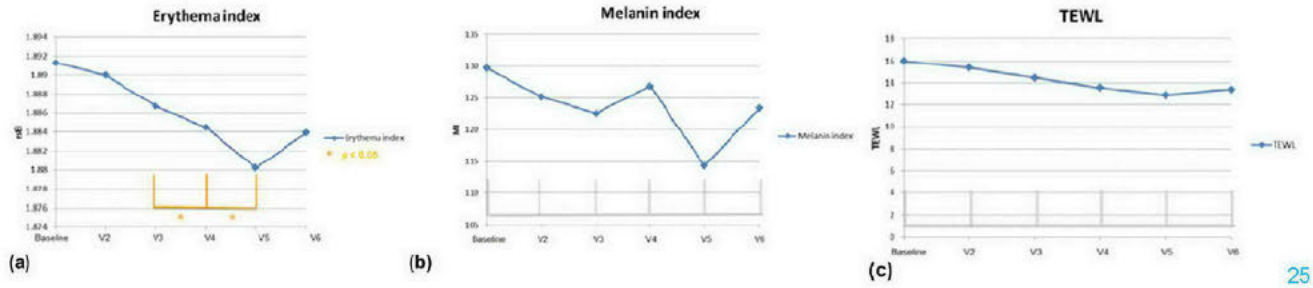
Results

- Most patients showed clinical improvement, as assessed by investigator's global assessment and patient global assessment scores.
- Erythema was significantly improved even after just one treatment and improvement was maintained until the sessions of treatment.
- Melanin index and transepidermal water loss (TEWL) showed a tendency toward improvement.
- The initial improvement in pores and smoothness was subtle, but was significant at the 4th and 5th visits.
- There were no serious adverse events reported during the study.



(A) Baseline (B) Post-treatment of 3 successive treatments

(C) Baselinet (D) Post-treatment of 3 successive treatments



VIOL-00000240

Ex. 2044-025

CX-2855C.25

Pulsed Wave: Vascular Lesion



Invasive Pulsed-Type, Bipolar, Alternating Current Radiofrequency Treatment Using Microneedle Electrodes for Nasal Rosacea

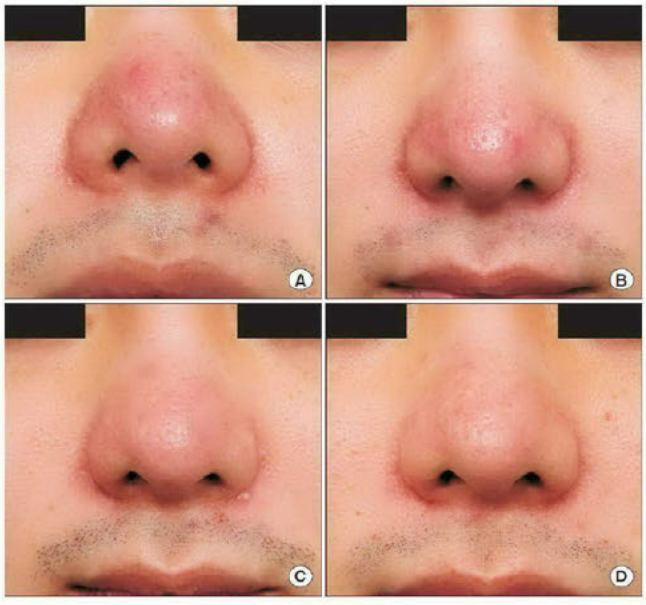
By Tae Hwan Ahn, and Sung Bin Cho
Medical Lasers, 2017, 6(1), 32-36:
http://doi.org/10.25289/ML.2017.6.1.32

Methods

- 2 Korean patients with nasal rosacea, were treated with invasive pulsed-type, bipolar alternating current RF using microneedle electrodes (SYLFIRM; ViOL) at 1.5mm, level 3, 2-3 passes.
  - First patient : male, 24-year-old, Fitzpatrick skin type IV / localized, recurrent erythematous papulopustular lesions on the nose, along with a few pustules on the perioral area / 6 sessions at 2-week intervals
  - Second patient : male, 76-year-old, Fitzpatrick skin type IV / markedly telangiectatic lesions on a mildly phymatous nose / 12 sessions at 2-week intervals

Results

- The first patient presented marked clinical improvement with respect to both the overall redness and papulopustular lesions.
- The second patient exhibited noticeable improvement in both the texture and telangiectatic lesions on the nose.
- No remarkable side effects, including immediate excessive bleeding or oozing, worsening of the nasal rosacea, folliculitis or furuncle, post-therapy prolonged erythema, post-therapy dyschromia, or scarring, were reported.



Papulopustular rosacea along the nose in a 24-year-old man
(A) Baseline
(B) 2 sessions
(C) 4 sessions
(D) 4 weeks after 6 sessions of RF microneedling treatment



Erythematotelangiectatic nasal rosacea in a 76-year-old man
(A) Baseline
(B) 2 weeks after 2 sessions
(C) 2 weeks after 7 sessions
(D) 4 weeks after 12 sessions of RF microneedling treatment

VIOL-00000241

Ex. 2044-026

CX-2855C.26

Pulsed Wave: Skin Rejuvenation



Laser-assisted Delivery of a Combined Antioxidant Formulation Enhances the Clinical Efficacy of Fractional Microneedle Radiofrequency Treatment: A Pilot Study

By Jihee Kim, Soo Min Kim, Bok Ki Jung, Sang Ho Oh, Young-Koo Kim, and Ju Hee Lee

Medical Lasers, 2021, 10(3), 161-169:

http://dx.doi.org/10.25289/ML.2021.10.3.161

Methods

- 6 women with mild to moderate photodamage, underwent a single session of a pulse-type fractional microneedling RF (FMRF) (SYLFIRM; ViOL) treatment and a topical formulation with L-ascorbic acid, vitamin E, and ferulic acid (LADD) for a split-face study.
  - Patient : mean age of 48.0 years, range of 35-57 years; Fitzpatrick skin types III-IV
  - One side: FMRF treatment only
  - The other side: FMRF treatment plus application of LADD
    - FMRF: 2.0-2.4mm, 100-150J
    - LADD: 4-5 drops
- Ex vivo, the full thickness human skin was used for molecular and histological evaluation: UVA, UVA+FMRF, UVA+FMRF+LADD.

Results

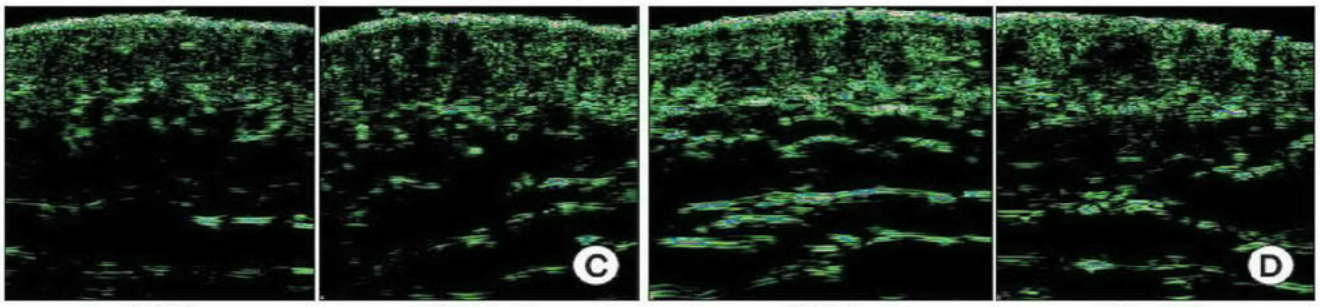
- The clinical signs of photorejuvenation, such as midface volume and dermal thickness, improved more on the treated side (FMRF+LADD) than on the untreated side (FMRF only) of the face.
- The difference in erythema between the sides was not statistically not significant.
- The histological data suggested that combining FMRF treatment with LADD of a formulation containing L-ascorbic acid, vitamin E, and ferulic acid leads to increased collagen synthesis.

VIOL-00000242

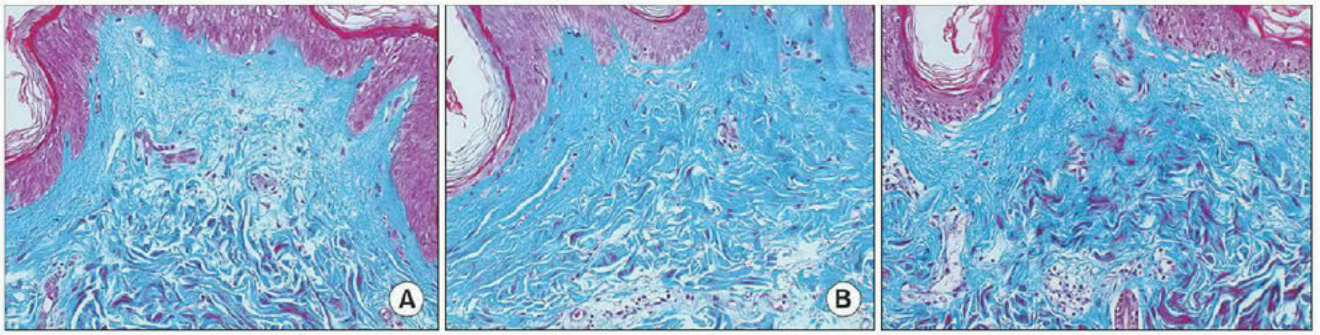
Ex. 2044-027

CX-2855C.27

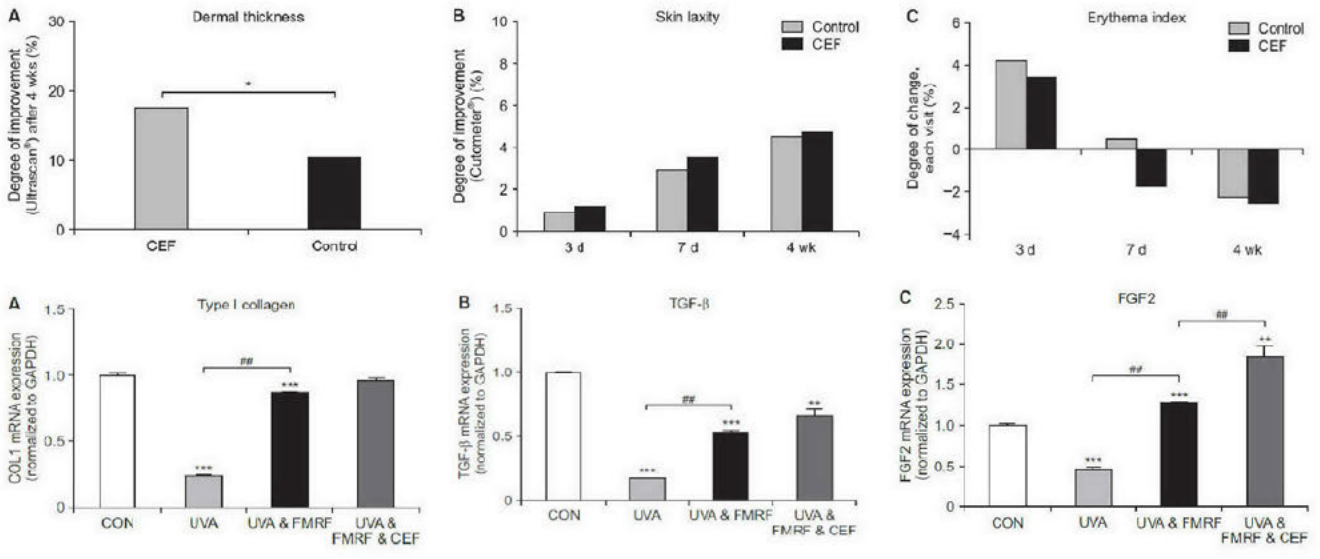
Pulsed Wave: Skin Rejuvenation



The increase in mean dermal thickness after 4 weeks, was higher on the treated side than that of the non-treated side. Ultrasound analysis.



The explanted skin exhibited increased COL3A1 expression after FMRF treatment. this expression was further increased after treatment with the antioxidant formulation. Masson's trichrome stain, x100.



*CEF: combined antioxidant formulation.
*TGF- β : transforming growth factor-b, a multifunctioning cytokine belonging to the transforming growth factor supefamily that includes three different mammalian isoforms and many other signaling proteins.
*FGF2: Basic fibroblast growth factor (bFGF) and FGF-β, a growth factor and signaling protein encoded by the FGF2 gene.
*COL3A1: collagen type III alpha 1 chain, provides instructions for making type III collagen

VIOL-00000243
Ex. 2044-028
CX-2855C.28

Pulsed Wave: Skin Rejuvenation



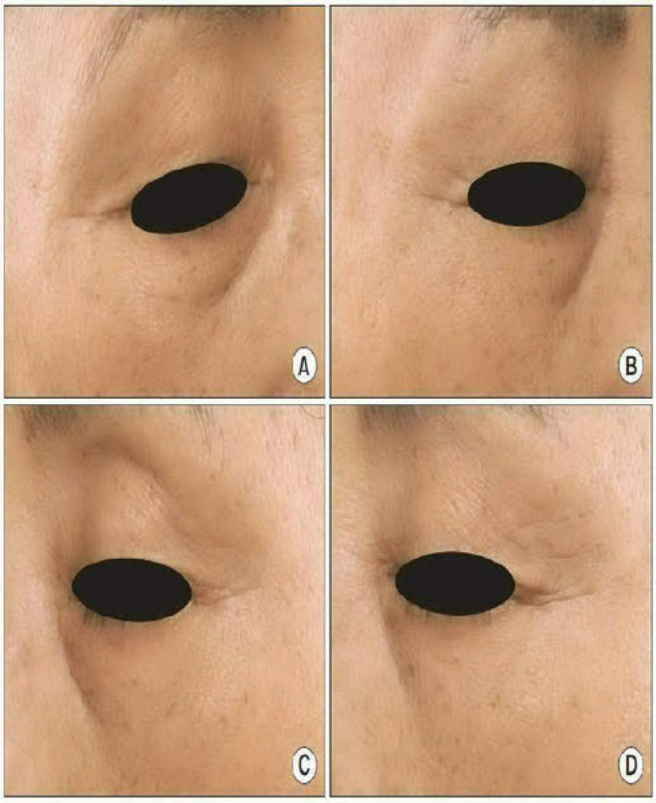
Improvement of Periorbital Wrinkles Treated with an Invasive Non-Insulated Microneedle Pulsed Electric Signal Device
By Suhyun Cho, Yoon Jin Choi, and Jin-Soo Kang
Medical Lasers, 2016, 5(1), 34-38:
http://doi.org/10.25289/ML.2016.5.1.34

Methods

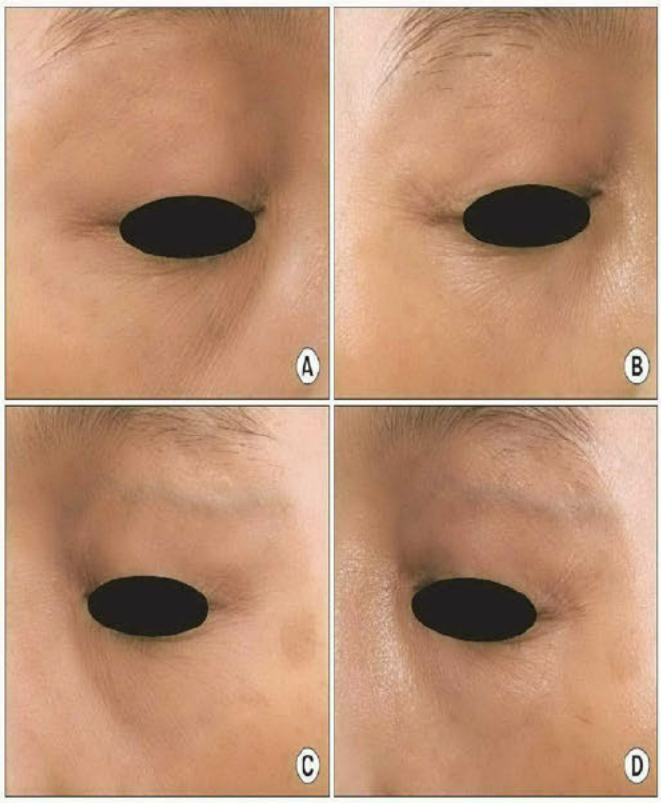
- 3 female Korea patients with variable degrees of periorbital wrinkles using an invasive non-insulated microneedle pulsed electric signal device (SYLFIRM; ViOL).
  - Treatment: 1.0-1.5mm, level 3-4, single pass, <10% overlap for 2 treatment sessions with 1 month interval

Results

- All patients showed objective improvements with their periorbital wrinkles with only 2 sessions and all accompanied patient's subjective satisfaction.
- Patients reported mild to moderate pain during the procedure.
- No noticeable side effects including epidermal shedding, crust formation or bruising was observed.



Many deep wrinkles nearly covering the entire periorbital area, with coarse wrinkles extending into the cheek
(A), (C) Before
(B), (D) 2 weeks after 2 sessions of RF microneedling treatment



Shallow wrinkles with some deeper wrinkles on the corner of the eyes
(A), (C) Before
(B), (D) 2 weeks after 2 sessions of RF microneedling treatment

VIOL-00000244
Ex. 2044-029
CX-2855C.29

Pulsed Wave: Scar



Adjuvant Therapy for Revision Rhinoplasty of Contracted Nose Using Polydeoxyribonucleotide and Invasive Bipolar Radiofrequency

By Tae Hwan Ahn, and Sung Bin Cho

Plastic and Reconstructive Surgery Global Open, 2018, 6(1), e1645:

http://doi.org/10.1097/GOX.0000000000001645

Methods

- 30 patients with contracted nose were treated with intralesional injection of PDRN and invasive RF using microneedle electrode (SYLFIRM; ViOL) before and after revision rhinoplasty and septoplasty.
  - Patients: 12 males and 18 females, a mean age of 37.7 years, ranging from 23 to 62 years
  - 8 preoperative sessions and 8 postoperative sessions at 1-week intervals
  - PDRN: a total amount of 0.3mL at 3 points using a 31-gauge, 1-mL insulin syringe
  - RF Treatment: 1.5mm, level 3, over 2-3passes

Results

- 1 week after the final combined pretreatment using PDRN and invasive bipolar RF, the skin of contracted noses was sufficiently softened, and nasal skin mobility was notably improved in all the patients.
- During revision rhinoplasty and septoplasty, the contracted nasal skin in each patient was adequately released for proper covering of the nasal tip without tension.
- Postoperatively, 8 sessions of adjuvant therapy elicited marked clinical improvements in persistent nasal tip dimpling and contracture, septal deviation, and warping from the incomplete recovery of nasal contracture after revision surgery.



(A) Baseline
(B) At 18 months after revision surgery with 8 sessions of preoperative and 8 sessions of postoperative adjuvant therapy



(A) Baseline
(B) At 18 months after revision surgery with 8 sessions of preoperative and 8 sessions of postoperative adjuvant therapy

[redacted] VIOL-00000245

Ex. 2044-030

CX-2855C.30

Pulsed Wave: Acne



Efficacy Assessment of a Pulsed Type Bipolar Radiofrequency Microneedling Device for Treating Facial Acne Vulgaris Using a Skin Color Imaging System: A Pilot Study **SCI(E) SCOPUS**

By TaeWoong Seul , Jong Heon Park, Jae Young Kim and Hwa Jung Ryu

Applied Sciences, 2023,13, 2114.

https://www.mdpi.com/2076-3417/13/4/2114

Methods

- Patients with acne were treated on both sides of their malar areas as well as their forehead using a pulsed-type bipolar radiofrequency device with non-insulated microneedles (SYLFIRM; ViOL) for three sessions, which were spaced at 4-week intervals (3 to 5 weeks).
  - Patients: 10 males and 8 females, a mean age of 22.7 years, ranging from 16 to 35 years
  - Five patients were taking oral antibiotics for acne
  - RF Treatment: 1.5mm, level 3, <10% overlap for 1-2passes

Results

- Almost all patients experienced significant decreases in the number and area of lesions after 3 sessions.
- During RF treatment and after the final treatment, side effects such as transient pain, tingling sensations, and erythema, were reported but they were mild and temporary, and temporary aggravation of acne vulgaris or folliculitis was not found.



(a) (b) (c)



(d) (e) (f)

1. Baseline: (a), (d)
2. After the second session: (b), (e)
3. After the third session: (c), (f)

VIOL-00000246

Ex. 2044-031

CX-2855C.31

300μm: Pigmented Lesion



Synergistic Effect of 300μm Needle-Depth Fractional Microneedling Radiofrequency on the Treatment of Senescence-Induced Aging Hyperpigmentation of the Skin

SCI(E) SCOPUS

By Young In Lee, Eunbin Kim, Dong Won Lee, Jemin Kim, Jihee Kim, Won Jai Lee, and Ju Hee Lee

International Journal of Molecular Sciences, 2021, 22(14), 7480: https://doi.org/10.3390/ijms22147480

Methods

- A split-face study was conducted using fractional microneedling radiofrequency (FMR) (SYLFIRM X; ViOL) and Q-switched 1064nm Nd:YAG laser toning (QSNY) in 25 Asian women with aging-associated hyperpigmentation.
- Patients: the mean age of 51.4±7.56 years, range 39-63 years, Fitzpatrick skin type III-IV, 11 with a single type of pigmentation, melasma and 14 with a mixed type of age-related hyperpigmentation, including melasma and senile lentigo
  - One side: QSNY + FMR
  - The other side : QSNY alone
    - QSNY: 6mm, 2.5-3.5J/cm², 10hz, 3 overlapping passes
    - FMR: PW2 mode, 300μm (0.3mm), level 4-6, 2 passes
    - 2 treatment sessions each week for a total of 5 weeks (weeks 0, 2, 4, 6, and 8)
- A human ex vivo study was conducted for immunohistochemistry and immunofluorescence: control, UVB, and UVB+FMR groups.

Results

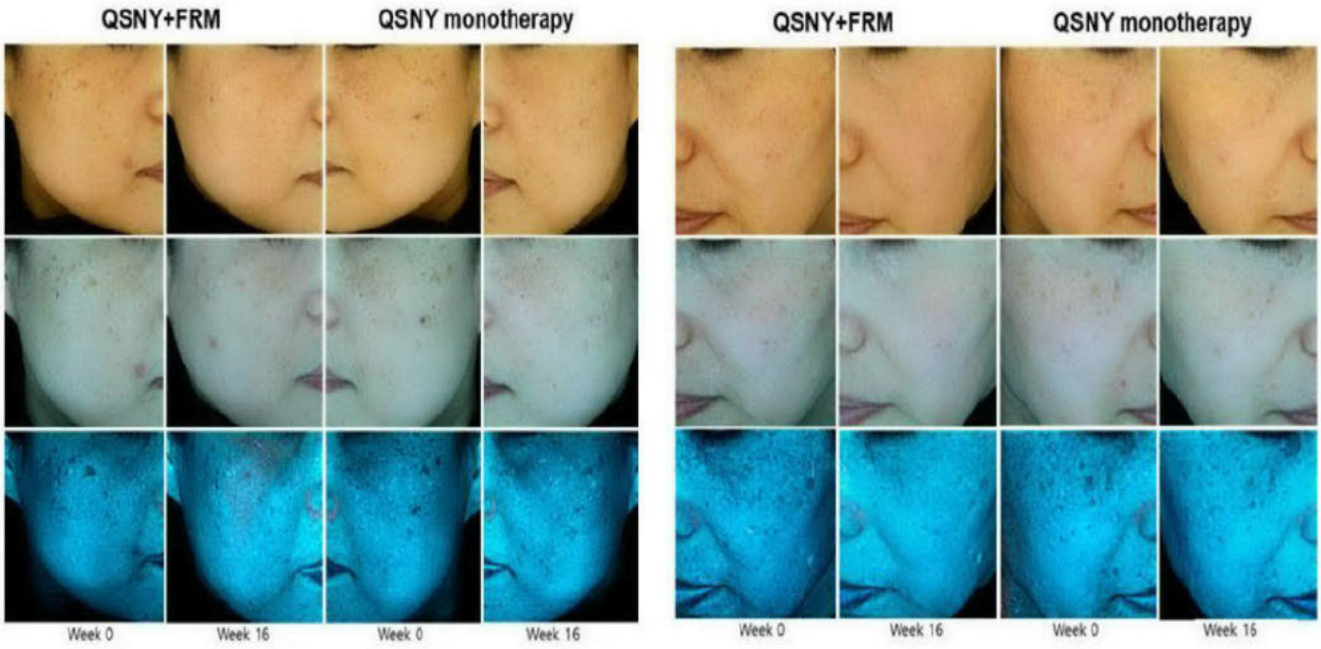
- The study showed significantly higher improvements not only on wrinkles, but also on hyperpigmentation.
- Additional ex vivo study revealed significant reduction of pro-melanogenic markers as well as senescent keratinocytes, while increased expression of collagen type IV on the epidermal basement membrane, after additional FMR treatment on UV-irradiated human tissues.
- These results demonstrate that 300μm needle-depth FMR might effectively remove senescent keratinocytes that secrete pro-melanogenic markers, and repair disrupted basement membrane, therefore preventing constant hyperpigmentation.

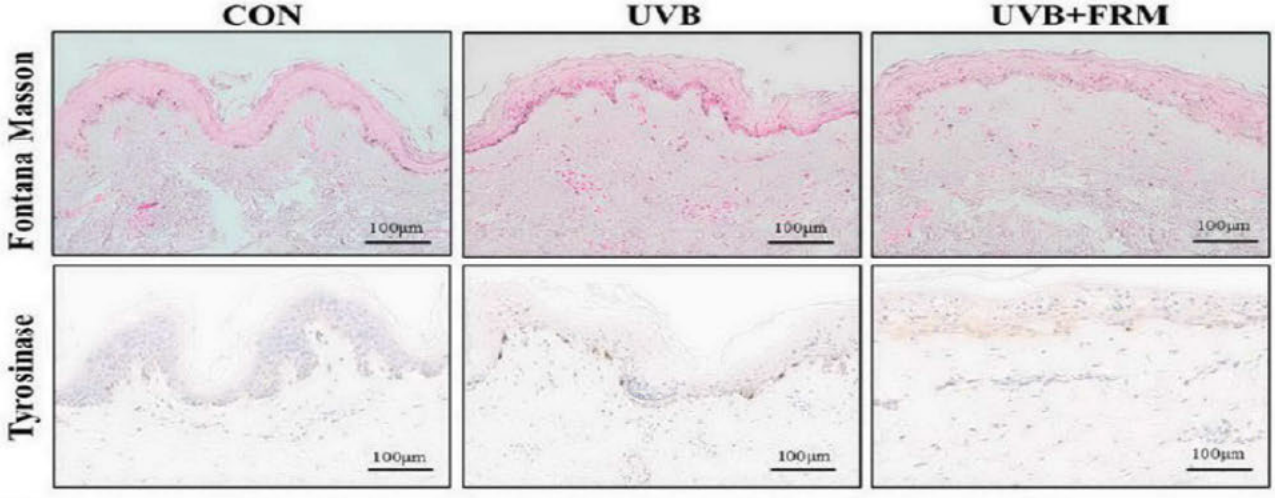
[redacted] VIOL-00000247

Ex. 2044-032

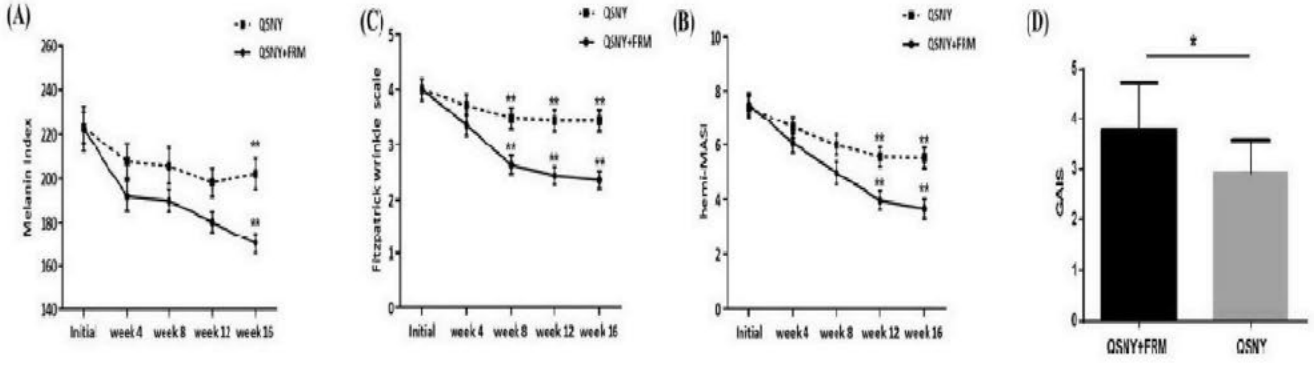
CX-2855C.32

300μm: Pigmented Lesion





*Tyrosinase : an enzyme that regulates the production of melanin and is involved in the reaction of melanin synthesis.



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