A Prospective Study of the Efficacy of Radiofrequency Micro Needling for the Treatment of Melasma in Skin of Color

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NCT06616311

Objectives

The objective of this study is to test the effectiveness of radiofrequency microneedling (RFMN) as a treatment for melasma. We hypothesize that RFMN will be an effective treatment for melasma in skin of color patients. The target population is skin of color patients with melasma. Patients will receive 5 consecutive RFMN treatments over a period of 5 months. Baseline melasma severity will be measured by the modified Melasma Area and Severity Index (mMASI) score. Endpoints will be mMASI scores at 1 and 3 months post-procedure. Patient reported outcomes will be measured using the melasma quality of life (MelasQOL) validated patient questionnaire at screening and at both follow up visits.

Study Subjects

Males or females, at least 18 years of age, with clinically diagnosed melasma and Fitzpatrick skin types IV-VI. Subjects must not be undergoing any current treatment for melasma, including both topical and oral treatments. A 6 week washout of all topicals (retinol, vitamin C serum, etc) except sunscreen prior to Day 1 (visit 2) will be required of all subjects. All subjects are recommended to wear daily tinted mineral sunscreen. Subjects must meet study criteria. A total of 10 subjects will be enrolled at one center, the Cleveland Clinic.

Duration of Study

The total duration of the subject participation in this study will be approximately 9 months and will include 5 procedure visits (at days 1, 30, 60, 90 and 120) over a span of 5 months, and 2 follow-up visits, 1 month and 3 months after the last procedure (at days 150 and 210).

Treatment procedures

Photographs will be taken prior to the start of procedure and at each subsequent visit. During each procedure visit, topical anesthesia will be applied without occlusion and left for approximately 30 minutes before initiation of the RFMN procedure. The RFMN tip will be passed over the treatment area for a total of up to three passes in alternating directions (vertically and horizontally). This process takes approximately 15 minutes.

Evaluation procedures

Treatment response will be evaluated by mMASI scoring of melasma severity at each visit. MelasQOL will be evaluated at first visit prior to RFMN treatment 1 and all following visits.

Significance

Melasma is an acquired disorder of hyperpigmentation. While the pathogenesis remains unknown, melasma usually occurs on sun-exposed areas of the skin, and ultraviolet radiation is considered the primary influencing factor; thus, recommended prevention measures include photoprotection using sunscreens. While melasma can occur in all populations, it is primarily seen in patients with Fitzpatrick IV-VI skin types. The reported prevalence of melasma ranges between 8.8-40%, depending on the ethnic makeup of the population (Neagu 2021). Melasma is a chronic cosmetic condition that can significantly affect both quality of life and self-esteem of the patients it impacts.

Current treatment options have varied and limited use and efficacy, and melasma is often refractory to treatment. Examples of these conventional care options include topical lightening agents such as hydroquinone, retinoids, and azelaic acid, as well as oral treatments such as tranexamic acid.

Given the limited treatment options for this chronic skin condition and its significant impact on quality of life, novel treatment modalities are necessary. Thus, there is growing demand for nonsurgical, noninvasive procedures for the treatment of melasma in patients with skin of color.

Radiofrequency (RF) energy devices have a well-documented safety profile with minimal post-treatment downtime and are widely used for skin rejuvenation. Radiofrequency microneedling devices pass a current through the dermis at various specified needle depths. This exposure to thermal energy creates a controlled skin injury, stimulating collagen production and dermal remodeling. While RFMN has shown clinical efficacy for skin rejuvenation in patients with skin of color, the use of these devices for the treatment of melasma in this patient population has not been robustly studied.

The possible benefit of this study will be the demonstration of RFMN as a clinically efficacious therapy for melasma in skin of color patients.

Introduction

Melasma is an acquired, chronic hypermelanosis that presents as irregular pigmented lesions due to melanin deposition in the skin. These lesions occur on sun-exposed areas of skin, usually on the face. The color of melasma can vary, ranging from light to dark brown to ashen gray. The precise pathogenesis of melasma remains unknown, with potential contributing factors including hormonal and genetic influences. The primary recognized factor is sunlight exposure. Melasma most commonly affects women of reproductive age and is most prevalent in Fitzpatrick skin types IV to VI. Melasma is considered a disfiguring condition that may severely affect facial appearance; thus, the need to treat comes from melasma's potential to significantly impact a patient's quality of life (Ali 2013). Current treatment options include topical lightening therapies such as hydroquinone, azelaic acid, retinoids, and corticosteroids, as well as oral therapies such as tranexamic acid. However, these therapies are varied and limited in both their use and efficacy. Due to limited treatment options for this chronic skin condition, novel treatment modalities that are nonsurgical and noninvasive, such as RFMN, are in growing demand.

The RFMN device used in this study is FDA-approved for use in dermatologic procedures for electrocoagulation and hemostasis. This device delivers a radio frequency signal to the target tissue using penetrating needle electrodes (**Figure 1**). As this signal passes through the skin, it generates heat to cause controlled damage to the skin, stimulating the production of new collagen. The ability to adjust needle depth and energy used allows the clinician to tailor the therapy to the patient's particular needs. As opposed to other laser therapy options for skin rejuvenation, RFMN is less likely to cause hyperpigmentation, and thus is considered safe for the darker skin types most commonly affected by melasma (Bhargava 2022, Tan 2021). However, there are few studies investigating the efficacy of these devices for the treatment of melasma in patients with skin of color.

In our proposed study, we will assess the change in mMASI scoring of melasma severity in patients who received 5 treatments of RFMN as dictated by our protocol. Specifically, patients will receive one RFMN session every 30 days for 120 days. Photographs and mMASI scoring will be collected at each visit.

The **study population** in our protocol will be adults with clinically diagnosed melasma. The **study endpoint** will be the efficacy of the treatment, as determined by change in mMASI scoring of melasma severity. Patient reported outcomes will also be evaluated using MelasQOL patient questionnaires at all visits. The **hypothesis** is that with RFMN, mMASI scores at 1 month and 3 months post procedure are significantly less than baseline mMASI scores, with minimal to no reported adverse events. The secondary hypothesis is there will be a reduction in MelasQOL scoring demonstrating an improvement in quality of life.

We will use an unblinded prospective pilot study design to determine efficacy with a minimal number of study patients. The prospective nature of this study provides many advantages including elimination of recall bias.

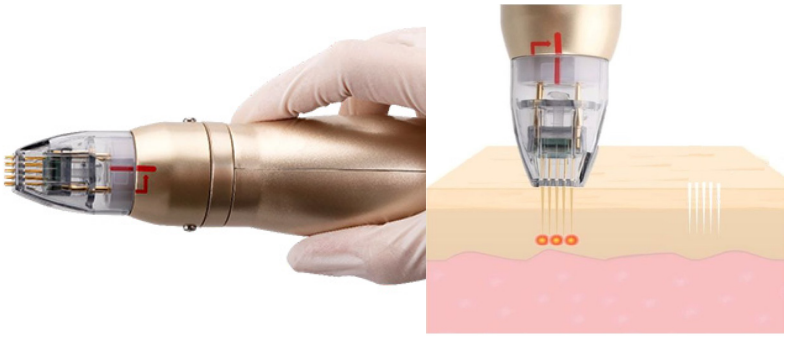

Figure 1: Using an electronically controlled hand piece, the system uses ultrafine needles to deliver radio frequency energy below the skin's surface (photo courtesy of SylfirmX)

Specific Aims

The specific aim of this study is to establish RFMN as an efficacious treatment for melasma in skin of color patients. The primary endpoint is treatment efficacy as determined by change in mMASI scoring of melasma severity post-treatment. The long-term goal of future studies would be to provide melasma patients, particularly those with skin of color, with improved therapeutic options for the treatment of their melasma, as compared to current treatment options.

Study Design and Methods

Recruitment

A maximum of 10 subjects will be enrolled in this study. Recruitment procedures include dermatology staff referring patients to study who are interested in procedural treatment for melasma. This study will be introduced to skin of color patients, who meet eligibility criteria, during their routine melasma visits with Dr. Khetarpal or Dr Murray. They will either be provided a copy of the consent form to take home and review or give permission to be contacted for more information regarding the study. If the study coordinator is available, they will briefly meet with the patient to provide copy of informed consent form and explain study design, and the patient will be instructed to review consent form and call study coordinator with any questions and/or if they would like to move forward with participation. If the study coordinator is not available to meet with the patient during their routine visit, they will be notified and will call the patient to explain the study and will also send a copy of the consent form via mail or email to the patient to review.

If a patient decides not to join the study for any reason, or if the patient otherwise does not fulfill criteria for the study (ex: Fitzpatrick skin type outside those specified in this study), the patient will be offered a standard-of-care procedure instead; this could be topical lightening agents such as hydroquinone, retinoids, and azelaic acid, as well as oral treatments such as tranexamic acid, and procedural treatments, such as thulium 1927nm laser.

Consent

Once the patient reviews the copy of the consent form that was provided by the study coordinator, either in person or via mail or email and the patient expresses interest in participating he/she will be scheduled for the first study visit. Once the patient arrives in clinic for Day 1, the study will be explained once again, along with the chance to ask additional questions, and if the patient indicates continuing willingness, then he/she will sign the consent form with the research coordinator and be considered enrolled. If a patient decides to not join the study for any reason or if they otherwise do not fulfill the criteria for the study, then the patient will be offered a standard-of-care treatment for melasma instead.

Study Subjects: Males or females with Fitzpatrick skin types IV-VI, at least 18 years of age, with preexisting clinically diagnosed melasma. Subjects must meet study criteria.

Duration of Study: The total duration of the subject participation in this study will be ~9 months and will include 5 procedure visits, and 2 follow-up visits.

Inclusion Criteria

- Males or females, at least 18 years of age
- Fitzpatrick skin types IV-VI
- Clinically diagnosed melasma
- No topicals (retinol, vitamin C serum, etc) for 6 weeks before Visit 1 (with exception of sunscreen)

Exclusion Criteria

Patients may be excluded from this study if he/she is:

- is currently pregnant or planning to conceive during the study period
- is using topical or oral therapy or other treatment for melasma

Use of tinted mineral sunscreen daily throughout the course of this trial is recommended to patients. Patients with history of HSV will be prophylactically treated with 1000 mg valcyclovir for 7 days starting 3 days before the procedure.

Treatment procedures: Subjects will arrive for Enrollment/Day 1 RFMN appointment. Pretreatment digital photographs will be taken and melasma severity will be measured using mMASI scoring of area of involvement and darkness. Subjects will complete the MelasQOL questionnaire. Next, topical anesthesia (lidocaine 23% and tetracaine 7% compound ointment) will be applied without occlusion and left for approximately 30 minutes before initiation of the procedure. RFMN will be performed on treatment areas. Subjects will undergo 5 consecutive RFMN treatments, 30 days apart (on Day 1, Day 30, Day 60, Day 90, and Day 120).

Post treatment: Patients will be asked to not apply anything on their face for 6 hours after each treatment. Starting that evening they can apply moisturizers and a gentle cleanser. The following day patients will resume use of tinted mineral sunscreen. The subject will return for 2 follow up visits at days 150 and 210 for photographs and clinical exam, during which melasma severity will be measured using mMASI scoring and patient outcomes will be measured using MelasQOL survey.

Table of Study Procedures

Summary of Activities	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
	Enrollment/ RFMN treatment 1	**RFMN treatment 2**	**RFMN treatment 3**	**RFMN treatment 4**	**RFMN treatment 5**	**Follow-up**	**Follow-up**
Scheduled Visit: → Procedure: ↓	**Day 1** (±7 days)	**Day 30** (±7 days)	**Day 60** (±7 days)	**Day 90** (±7 days)	**Day 120** (±7 days)	**Day 150** (±7 days)	**Day 210** (±7 days)
Informed Consent	X						

Patient Demographics (age, sex, Fitzpatrick skin type)	X						
Clinical Exam: mMASI scoring	X	X	X	X	X	X	X
MelasQOL: Patient questionnaire	X	X	X	X	X	X	X
RFMN	X	X	X	X	X		
Photography	X	X	X	X	X	X	X

Standard of care: RFMN is not the standard of care. Any melasma remaining after visit 7 will be treated with standard care.

Privacy and confidentiality: The medical information obtained in this study will remain in the regulatory binder for the study and housed in a locked research office only accessible by the research team. All information contained in the subject's record will remain confidential and will only be viewed by the principal investigator and research team.

The results of this study may be published in a medical research journal or book or used for teaching purposes. The participant's name or pertinent information will not be used. Photographs taken during the study will be kept in the subject's file. Some photos may be shared with the sponsor. Consent to allow use of those images in medical publications or presentations that result from the study is voluntary, as the patient will indicate in a checkbox. Personal information will be removed before results are reported. However, it may not be possible to alter the photos to hide patient's identity since lesions are on the face.

Interpretation of Data

Study Endpoints: The primary endpoint in this study is to determine the change in mMASI scoring of melasma severity before intervention, at day 150, and at day 210. The secondary endpoint is the change in patient reported outcomes using MelasQOL survey prior to first treatment at day 1 and at follow up visits at days 150 and 210.

Evaluation procedures:

Patient demographics (age, sex, Fitzpatrick skintype) will be obtained.

Clinical Assessment of Response of Melasma after Treatment

mMASI SCORING: Melasma severity will be evaluated using mMASI scoring at all study visits. Additional details about the appearance of the treatment area, and associated clinical features (i.e., hyperpigmentation or scarring) will be assessed for and recorded at each visit.

MelasQOL Survey: Patient reported outcomes will be evaluated using MelasQOL survey at each visit, prior to intervention on treatment days.

PHOTOGRAPHY: Photographs of the treatment areas will be obtained at all study visits.

Data management:

Study patients will be identified only by patient Study ID number, and their data stored in a password-encrypted REDCap database accessible only be members of the study team.

DATA STORAGE:

- Primary clinical data from each encounter will be stored in REDCap.
- Digital photographs will be stored in Mirror Medical Imaging Software.

DATA TO BE RECORDED
The following lists individual parameters that will be recorded in REDCap.

VISIT 1, DAY 1 (Enrollment and Treatment visit):

Record ID

Study ID

Visit date

Inclusion criteria: Adults at least 18 years old; Fitzpatrick skin types IV-VI; clinically diagnosed melasma

Exclusion criteria: Pregnant or planning to conceive; uses topical or oral therapy for melasma

Age

Sex: Male/Female

Fitzpatrick skin type

Consent form signed: YES/NO

Clinical exam done: mMASI scoring

MelasQOL survey

Photographs taken: YES/NO

Topical anesthetic applied: YES/NO

RFMN performed: YES/NO

Aftercare instructions given: YES/NO

VISIT 2 DAY 30 (Treatment Visit):

Visit date

Photographs in studio taken: YES/NO

MelasQOL survey

Patient reported adverse event?

Patient notes improvement? If yes, what percentage improvement?

Clinical exam done: mMASI scoring

Topical anesthetic applied: YES/NO

RFMN performed: YES/NO

Aftercare instructions given: YES/NO

VISIT 3 DAY 60 (Treatment Visit):

Visit date

Photographs in studio taken: YES/NO

MelasQOL survey

Patient reported adverse event?

Patient notes improvement? If yes, what percentage improvement?

Clinical exam done: mMASI scoring

Topical anesthetic applied: YES/NO

RFMN performed: YES/NO

Aftercare instructions given: YES/NO

VISIT 4 DAY 90 (Treatment Visit)

Visit date

Photographs in studio taken: YES/NO

MelasQOL survey

Patient reported adverse event?

Patient notes improvement? If yes, what percentage improvement?

Clinical exam done: mMASI scoring

Topical anesthetic applied: YES/NO

RFMN performed: YES/NO

Aftercare instructions given: YES/NO

VISIT 5 DAY 120 (Treatment Visit)

Visit date

Photographs in studio taken: YES/NO

MelasQOL survey

Patient reported adverse event?

Patient notes improvement? If yes, what percentage improvement?

Clinical exam done: mMASI scoring

Topical anesthetic applied: YES/NO

RFMN performed: YES/NO

Aftercare instructions given: YES/NO

VISIT 6 DAY 150 (30-day post-treatment follow-up Visit):

Visit date

Photographs taken: YES/NO

Clinical exam done: mMASI scoring

MelasQOL survey

Patient reported adverse event?

Patient notes improvement? If yes, what percentage improvement?

VISIT 7 DAY 210 (90-day post-treatment follow-up Visit):

Visit date

Photographs taken: YES/NO
Clinical exam done: mMASI scoring

MelasQOL survey

Patient reported adverse event?

Patient notes improvement? If yes, what percentage improvement?

Data Analysis (Analytical approach and interpretation)
TREATMENT EFFICACY: mMASI scoring of melasma severity will be performed at screening/enrollment, prior to treatment on each procedure visit, and on both follow-up visits. Treatment efficacy will be measured as the difference (reduction) in mMASI score from day 1 to days 150 and 210.

MelasQOL survey of patient reported outcomes will be performed at all visits. Patient reported improvement will be measured as the difference (reduction) in MelasQOL score from day 1 to days 150 and 210.

Statistical Calculations
Sample size was determined using a sample size calculator for comparing 2 proportions, assuming the following: 95% confidence level, 80% power, the likely proportion of untreated patients developing improvement is 0%, and the likely proportion of treated patients developing improvement is 50%. **A sample size of 8 patients will allow us to determine the efficacy of this treatment based on change in mMASI scoring.**

Device Safety, Data Monitoring, and Reporting of Adverse Events

Device safety and procedural risks

SIDE EFFECTS OF RADIOFREQUENCY MICRONEEDLING (RFMN)

Possible side effects are mild erythema and edema. For patients with history of HSV infection, HSV flare may occur, therefore prophylactic treatment will be provided for every patient with history pf HSV.

The device used in this study is FDA-approved; however, not for the indication of melasma. Thus, this study is being conducted to assess efficacy of its use in the treatment of melasma. Adverse events are extremely unlikely and are limited to cosmetic side effects (i.e., hyperpigmentation or scarring).

Adverse events reporting

Patients will be notified of possible adverse outcomes prior to enrollment in this study via a detailed informed consent document. Affirmative responses will prompt investigation by a study physician with subsequent referral to the IRB according to the published CCF IRB Policies and Procedures Manual.

References

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