Project Title: Safety and Efficacy of High-Intensity Macrofocused Ultrasound for Solar Lentigo in Chinese Population: A Prospective Study

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I. Background

Solar Lentigo (SL), also known as solar lentigines, or age spots, is a skin disorder associated with photoaging. It primarily appears as irregular gray or dark brown patches with a smooth surface and clear borders. Solar lentigo commonly occur in sun-exposed areas, such as the face, neck, hands, and forearms, potentially affecting appearance and causing psychological stress for patients. Current treatment options include laser, cryotherapy, chemical peeling, topical medications, and combination therapies. Among these, laser therapies, particularly Q-switched lasers, are considered the most effective single therapy, as they can precisely target treatment areas through selective photothermolysis. However, this method is influenced by skin color and carries risks of pain, redness, and hyperpigmentation.

High-Intensity Focused Ultrasound (HIFU) is a technique that focuses high-frequency ultrasound on selected tissue areas within the body. By utilizing thermal effects, cavitation effects, and mechanical effects, HIFU can create instantaneous temperatures exceeding 65°C in the focal zone, stimulating collagen regeneration and remodeling, thus achieving skin tightening. It is widely used in skin rejuvenation treatments. Both micro- and macro-focused ultrasound have been shown to be effective non-invasive treatments for skin rejuvenation. Recent studies have shown that HIFU can significantly reduce UVB-induced epidermal melanin deposition, a finding confirmed in animal models of melasma and clinical studies. This effect may be related to the vibration and friction of the pigment caused by ultrasound, mechanically disrupting and eliminating melanin and pigment fragments in the superficial epidermis and dermis. Moreover, the absorption of ultrasound energy does not rely on skin pigmentation, which can reduce adverse reactions in individuals with darker skin tones, suggesting that HIFU may serve as an alternative treatment for solar lentigo.

II. Objective

Primary Objective: This study aims to evaluate the efficacy and safety of high-intensity macro-focused ultrasound in treating facial solar lentigo, as well as its additional effects on the skin using both subjective and objective assessment methods.

III. Study Design:

This study was a prospective, single-center trial, recruited from the First Affiliated Hospital of Nanjing Medical University from November 2023 to February 2024. This trial was approved by the ethics committee (No. 2023-SR-708). All participants have signed written informed consents.

The treatment involves using two ultrasound devices with different focal depths of 3.0 mm (D3.0) and 4.5 mm (D4.5) (MFUS One, Hunan Peninsula Medical Technology Co., Ltd., China) on both sides of the face. After the procedure, an ice pack will be

applied to the treated area for 10 minutes to help reduce redness and swelling. Follow-up visits will be scheduled at 2, 4, 6, and 8 weeks after the treatment. During these visits, clinical images and non-invasive skin assessments will be conducted to monitor your progress.

IV. Study Population

Inclusion Criteria:

1.adults between 18 and 70 years old, regardless of gender;

2.those who comply the clinical diagnostic criteria for solar lentigo on both sides of the face;

3.patients understand and are willing to participate in this clinical trial and voluntarily sign an informed consent form;

Exclusion Criteria:

1.Women who are pregnant or breastfeeding, or who plan to become pregnant during the trial period;

2.those who are allergic to medical condensation gel;

3.those with photosensitive diseases, immune deficiencies, or those who are taking immunosuppressants;

4.those with scar physique;

5.those with inflammatory or infectious skin diseases;

6.those who have systemically used retinoic acid in the last six months or topically applied retinoic acid drugs in the last three months, or have a history of sun exposure in the four weeks prior to treatment;

7.those who have undergone high-intensity focused ultrasound treatment within the last six months;

V. Procedures

Before the treatment, a 2-3mm layer of medical cooling gel will be evenly applied to your face. Two macro-focused handpieces with focal depths at 3.0 mm (D3.0) and 4.5 mm (D4.5) were employed on both cheeks (MFUS One, Hunan Peninsula Medical Technology Co., Ltd., China), targeting both the lesional area and surrounding non-lesional regions while avoiding the periorbital and perioral areas. After the procedure, an ice pack will be applied to the treated area for 10 minutes to help reduce

redness and swelling. Follow-up visits will be scheduled at 2, 4, 6, and 8 weeks after the treatment. During these visits, clinical images and non-invasive skin assessments will be conducted to monitor the improvement. For non-invasive skin assessment, skin elasticity (R-value) and transepidermal water loss (TEWL) were measured using a Cutometer Dual MPA580 (Courage Khazaka Electronic GmbH, Köln, Germany) and Tewameter Hex (Courage Khazaka Electronic GmbH, Köln, Germany), respectively.

VI. Outcome Measures

1. Primary Outcome

Title: Lab* Values of Lesional Area Using Dermoscopy and ImageJ

Description: This outcome measure involves the assessment of lesional areas in dermoscopy images, with the Lab* conversion of pigmentation intensity performed using ImageJ software. L represents the lightness (brightness) of the lesion, where higher L values indicate lighter lesions (improvement). a and b represent the chromatic components (red-green and yellow-blue). Lower values in these components indicate lighter pigmentation, while higher values suggest darker lesions.

Time Frame: week0, week2, week4, week6 and week8

2. Primary Outcome

Title: Physician Global Aesthetic Improvement Scale

Description: The Physician Global Aesthetic Improvement Scale (PGAIS) is a 5-point scale used to rate the global aesthetic improvement in appearance compared to baseline, as judged by the investigator. The scale ranges from -1 (worsening) to 3 (very much improved). The higher score indicates the better improving effect.

Time Frame: week2, week4, week6 and week8

3. Primary Outcome

Title: Subjective Global Aesthetic Improvement Scale

Description: The Subjective Global Aesthetic Improvement Scale (SGAIS) is a 5-point scale used to rate the global aesthetic improvement in appearance compared to baseline, as judged by the patients. The scale ranges from -1 (worsening) to 3 (very much improved). The higher score indicates the better improving effect.

Time Frame: week2, week4, week6 and week8

4. Primary Outcome

Title: Transepidermal Water Loss (TEWL) Measurement of Lesional Area

Description: This outcome measure involves the assessment of transepidermal water loss (TEWL), which quantifies the amount of water evaporating through the skin. TEWL is a key indicator of skin barrier function and hydration levels. In this study, TEWL was measured using Tewameter Hex (Courage Khazaka Electronic GmbH) that records the rate of water loss through the skin in $g/m^2/h$ (grams per square meter per hour). Lower TEWL values (less water loss) suggest an improved skin barrier, which is typically the result of effective treatment and increased skin hydration.

Time Frame: week0, week2, week4, week6 and week8

5. Primary Outcome

Title: Skin Elasticity Measurement of Lesional Area

Description: Skin elasticity was assessed using Cutometer Dual MPA580 (Courage Khazaka Electronic GmbH, Köln, Germany), which measures the skin's resistance to deformation and recovery after deformation. The R-value represents the ratio of skin's ability to resist deformation and its ability to return to its original shape Higher R-values (greater elasticity) suggest that the skin is more resilient and can return to its original shape after deformation, indicating healthy skin with good elasticity and tone.

Time Frame: week0, week2, week4, week6 and week8

IV. Statistical Analysis:

For dermoscopy images, ImageJ software was utilized to perform Lab* conversion on both the lesional and surrounding non-lesional areas. The skin elasticity (R-value), TEWL, skin chroma (Lab* values), and Global Aesthetic Improvement Scale (GAIS) scores were analyzed using repeated-measures analysis of variance (RM-ANOVA) with Greenhouse-Geisser correction to evaluate the statistical significance of treatment effects over time. When interaction effects were observed, simple effects analysis was performed to identify the specific source of the interaction. In cases where no interaction effects were found, the main effects were analyzed. Statistical significance was set at $p < 0.05$ (two-tailed). All statistical analyses were conducted using SPSS Statistics for Windows (version 26.0; IBM Corp.).