

## ORIGINAL CONTRIBUTION

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# Nitrogen plasma skin regeneration for the treatment of mild-to-moderate periorbital wrinkles: A prospective, randomized, controlled evaluator-blinded trial

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**Summary**

**Background:** Nitrogen plasma skin regeneration is a novel device that produces heat to the skin, resulting in the production of new collagen. Because of lower energy with safer skin damage and lesser adverse effects who have high Fitzpatrick's skin type especially Thais, this technique is very interesting for clinical application for skin esthetic treatment. However, this treatment has yet been empirically studied as the treatment for mild-to-moderate periorbital wrinkles.

**Objectives:** This study aimed to evaluate clinical efficacy of nitrogen plasma for the treatment of mild-to-moderate periorbital wrinkles.

**Methods:** Eighteen volunteers were enrolled. Each volunteer was randomized to receive nitrogen plasma treatment on one side of periorbital wrinkles with three sessions at a three-week interval and compared with contralateral side without treatment. Photographic examination, skin wrinkle (SEw) score, melanin index, patients' satisfaction score, side effect, and pain score were reported.

**Results:** At over fourteen weeks, all volunteers completed the study. Treatment with nitrogen plasma group had significantly better improvement for periorbital wrinkles score by Lemperle scale, skin wrinkle (SEw) score by Visioscan® VC 98, and the melanin index by Mexameter® than the control groups ( $P = 0.004$ ,  $P < 0.001$ ,  $P < 0.001$ , respectively). This study also showed significantly greater satisfaction score to favor the nitrogen plasma treatment group than the control group ( $P < 0.001$ ). The short-term adverse effects included erythema, scaling, temporary hyperpigmentation, pruritus, and dryness.

**Conclusion:** Nitrogen plasma skin regeneration is effective and safe for the treatment of mild-to-moderate periorbital wrinkles and darkening.

**KEYWORDS**

nitrogen plasma, periorbital darkening, periorbital rejuvenation, periorbital wrinkles, plasma skin regeneration

## 1 | INTRODUCTION

Aging is a natural process which occurs throughout the body's systems. One of the most visible signs of aging skin is often shown in the periorbital area. This is usually the first clinical presentation of facial aging.<sup>1</sup> Eyelid skin is the thinnest in the body.<sup>2,3</sup> Presently, there are many optional procedures for treating periorbital wrinkles, such as applying topical drugs with retinoids, chemical peeling with glycolic or trichloroacetic acid, microdermabrasion, botulinum toxin, filler injection, laser, nonlaser method, and surgery.<sup>1,4–9</sup> Nevertheless, there is currently no standard treatment. The preferred choice of treatment depends on individual causes, severity, Fitzpatrick skin type, downtime of treatment, and socioeconomic status.

A technology known as plasma skin regeneration (PSR), approved by the Food and Drug Administration (FDA), is a method whereby plasma energy is used to create thermal effect to the skin. This technology was first invented by Rhytec, Inc (Waltham, MA, USA), currently owns by Energist Group (Swansea, UK). It is induced by passing radiofrequency into nitrogen gas to create plasma: the fourth state of matter, in which electrons are stripped from atoms forming ionized gas. The electrons are then recaptured by positively charged atoms at the same time with energy emitted in a millisecond pulse to the targeted skin, in the form of heat without chromophore dependence. This induces controlled thermal damage in the skin, which results in a production of new collagen and a restructuring of dermal architecture. PSR can be used at various energy settings depending on targeted depths, such as acne scars, skin laxity, photoaging skin, clearance of superficial skin lesions, actinic keratosis, and seborrheic keratosis. Each pulse of plasma energy is released to the treated area in a Gaussian distribution creating an inner zone of thermal damage and an outer zone of thermal modification.<sup>10–15</sup> Owing to the relatively low thickness of eyelid skin, the low energy of nitrogen plasma may be suitable for eyelid area. The low energy of nitrogen plasma is also safer and has less adverse effects for Thais who have high Fitzpatrick skin type due to the PSR's properties of nonchromophore dependence. However, the treatment with low energy of nitrogen plasma has yet been empirically studied as the treatment for mild-to-moderate periorbital wrinkles in Thai population.

## 2 | MATERIALS AND METHODS

This is an experimental, prospective, randomized, controlled evaluator-blinded trial. Eighteen Thai volunteers with mild-to-moderate periorbital wrinkles were enrolled by the calculated PS sample size program (version 3.0) according to the previous study of Chang et al.<sup>8</sup> The study was conducted from February 9, 2017, to June 9, 2017, at the Skin Center and was approved by the Clinical Research Ethical Committee. All volunteers were informed about procedures, risks, benefits, and adverse effects. Informed consent was obtained from every volunteer. Each volunteer was randomized to receive treatment on one side of periorbital wrinkles with three sessions of nitrogen plasma at a three-week interval, while the other side of periorbital wrinkles was left untreated during the study period.

### 2.1 | Inclusion criteria

The volunteers aged between 20 and 50 years old with mild-to-moderate periorbital wrinkles based on Lemperle scale (score 0–3).<sup>16</sup>

### 2.2 | Exclusion criteria

Volunteers who had uncontrolled systemic disease or active skin disease that could interfere with the evaluation of the treated areas, photosensitivity, vitiligo, tendency to develop keloid, pregnancy, and lactation. Volunteers who previously applied topical tretinoin, alpha hydroxy acids, or took oral retinoids within 6 months before the beginning of the study. Volunteers who were treated with ablative laser, other lasers, chemical peeling, botulinum toxin or filler injection, or dermabrasion within six months prior to the study. Volunteers who were unable to follow-up to the study protocol.

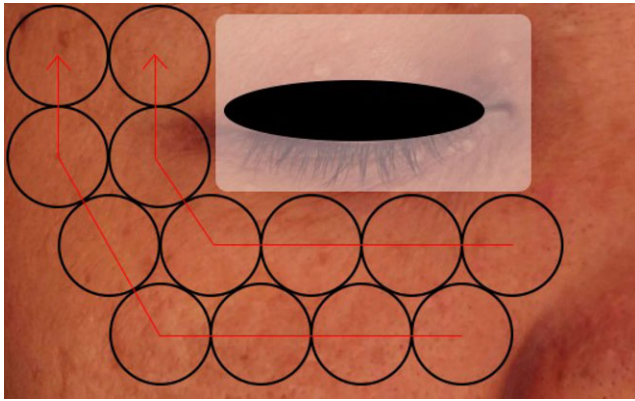
### 2.3 | Treatment protocol

Each volunteer was randomized to receive treatment on one side of periorbital wrinkles with three sessions of nitrogen plasma (NeoGen™ Spa; Energist Group, Swansea, UK) at 3-week intervals, using 0.8 J pulse energy with the pulse duration of 6.6 ms in 1 Hz. The 12-mm spot size and the 25-mm plasma outlet tube contacted the entire periorbital area in two passes and two rows in a nonoverlapping way and perpendicularly. Movement of the handpiece always follows the same direction because of the uniform heating (Figure 1). Prior to the treatment, each treated area was cleaned by gentle cleansing. Subsequently, topical hydrated moisturizer (Cetaphil Daily Advance Ultra Hydrating Lotion; Galderma Laboratories) was applied for 30 minutes and then was wiped off with dry gauzes immediately before the treatment. To protect the eyes and lashes, volunteers were asked to close and cover their eyes with dry gauzes. For post-treatment skin care, all volunteers were required to apply a hydrated moisturizer (Cetaphil Daily Advance Ultra Hydrating Lotion; Galderma Laboratories) and sunscreen (Spectraban spf 50+; Stiefel Laboratories), and to avoid sun exposure for both two periorbital areas during the study period.

### 2.4 | Outcome evaluation

The clinical evaluation with photographic examination by two independent, blinded dermatologists was determined at baseline, in the third week, the sixth week, and the endpoint evaluation visit at fourteenth week by using Olympus E-3 camera and digital photograph (CLREO-I; YKCTECH, Kyungsangnamdo, Korea). The severity of wrinkle was evaluated based on Lemperle scale with grading scores ranging between 0–5 (0 = no wrinkle, 1 = just perceptible wrinkles, 2 = shallow wrinkles, 3 = moderately deep wrinkles, 4 = deep wrinkles, well-defined edges, 5 = very deep wrinkles, redundant fold).

The average periorbital wrinkles were measured twice by UVA-light video camera (Visioscan® VC 98; Courage & Khazaka Electronic, Cologne, Germany) with the analysis software [Surface



**FIGURE 1** To demonstrate the movement of handpiece in the same direction for the uniform heating. Eyelash and eyebrow covered with dry gauze

Evaluation of the Living Skin; skin wrinkle (SEw)]. The average melanin index was measured twice by Mexameter® MX 18 (Courage & Khazaka Electronic, Cologne, Germany). The landmark of these instruments was designated at periorbital area; right under and 2 cm lateral from mid-pupil.

In addition, satisfaction scores of volunteers were evaluated on each visit using 5-point scale (1 = very dissatisfied, 2 = not very satisfied, 3 = slightly satisfied, 4 = satisfied, 5 = very satisfied). The adverse effects were also recorded on each visit. The pain score was evaluated using a 10-point visual analog scale.

## 2.5 | Statistical analysis

Statistical data analysis was done by the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 19.0. The categorical variables were reported as frequencies and percentages, while the continuous variables were reported in a form of mean  $\pm$  standard deviation (SD). For inferential statistics, Shapiro-Wilk test was used to test the distribution of the data. If the data had normal distribution, so independent *t* test was used to compare the average mean for baseline between the treatment group and control group. The analysis of covariance (ANCOVA) test was used to compare the average mean changes from baseline between two groups at different time point and at endpoint visit. The chi-squared or Fisher's exact test was used to compare the categorical data between two groups. A *P*-value of 0.05 or less was interpreted as statistical significance.

## 3 | RESULTS

### 3.1 | Demographic data

At over fourteen weeks, eighteen (100%) volunteers completed the study. Sixteen (88.9%) patients were female and two (11.1%) patients were male. The average mean age  $\pm$  standard deviation (SD) was  $39.3 \pm 8.4$  years. Nine volunteers were classified as Fitzpatrick

skin type III, and the others were classified as Fitzpatrick's skintype IV. Seven volunteers had mild periorbital wrinkles, and eleven volunteers had moderate periorbital wrinkles.

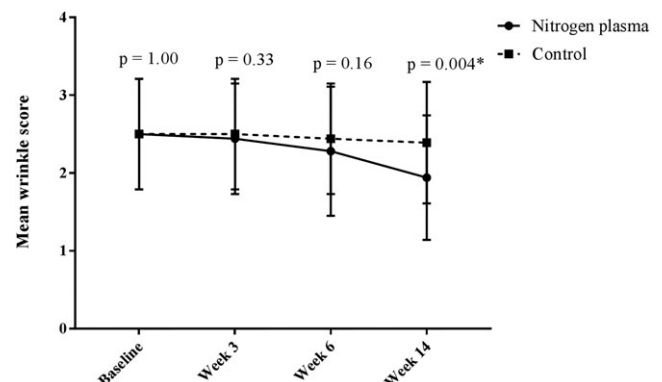
### 3.2 | Outcomes

The mean wrinkle score, assessed by two blinded dermatologists, was not different at baseline between the two groups. In the treatment group, the mean wrinkle score at baseline was  $2.5 \pm 0.7$  and changed to  $1.9 \pm 0.8$  at 14-week visit. But in the control group, the mean wrinkle score at baseline was  $2.5 \pm 0.7$  and changed to  $2.3 \pm 0.7$  in the 14-week visit. The mean wrinkle score decreased from baseline in the treatment group more than the control group with statistically significant at 14-week visit ( $P = 0.004$ ) (Figure 2).

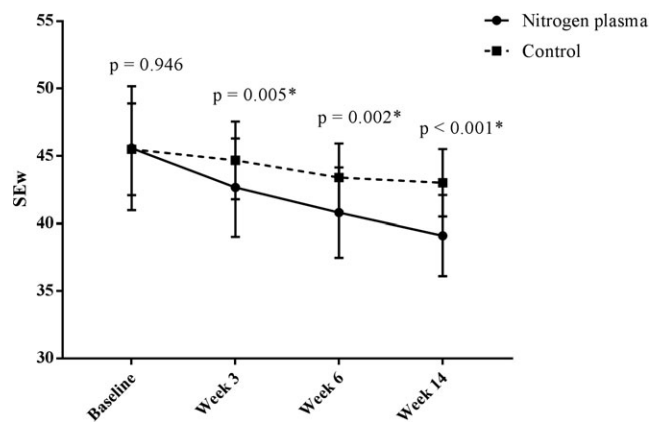
The mean skin wrinkle (SEw), measured by the Visioscan® VC98, showed no difference at baseline between two groups. In the treatment group, the mean SEw at baseline was  $45.5 \pm 4.6$  and changed to  $39.1 \pm 3$  at 14-week visit. But in the control group, the mean SEw at baseline was  $45.4 \pm 3.4$  and changed to  $43 \pm 2.5$  in the 14-week visit. The mean SEw showed more improvement in the treatment group than control group with statistically significant starting from 3-week visit through the 14-week visit ( $P < 0.05$ ) (Figure 3).

The mean melanin index, measured by the Mexameter® MX 18, showed no difference at baseline between two groups. In the treatment group, the mean melanin index at baseline was  $504 \pm 16.7$  and changed to  $481.8 \pm 13.2$  at 14-week visit. But in the control group, the mean melanin index at baseline was  $504.5 \pm 17.3$  and changed to  $495.4 \pm 14.3$  in the 14-week visit. The mean melanin index showed more improvement in the treatment group than a control group with statistically significant starting from the 3-week visit through the 14-week visit ( $P < 0.05$ ) (Figure 4). This study also showed significantly higher satisfaction scores among volunteers in the treatment group than the control group ( $P < 0.001$ ). The clinical improvement picture is shown in Figure 5.

The common short-term adverse effects of the nitrogen plasma groups included erythema, scaling, temporary hyperpigmentation,



**FIGURE 2** To demonstrate mean wrinkle score at baseline, 3-week, 6-week, 14-week visit of nitrogen plasma group and control group. \*Analysis of covariance (ANCOVA). *P*-value  $< 0.05$ , determined as significant value

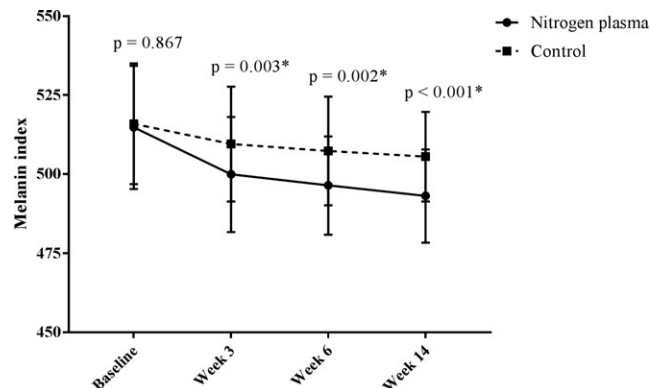


**FIGURE 3** To demonstrate mean wrinkle (SEw) at baseline, 3-week, 6-week, 14-week visit of nitrogen plasma group and control group. \*Analysis of covariance (ANCOVA). P-value < 0.05, determined as significant value

pruritus, and dryness. The number and duration of these adverse effects are shown in Table 1. The shortest duration among all the adverse effect was erythema (12 hours), and the longest duration was hyperpigmentation and desquamation (48 hours). All the adverse effects were mild and resolved without permanent skin change or scarring. The volunteers rated the pain scores at a mild level of severity (1-3 points).

#### 4 | DISCUSSION

Periorbital wrinkle is a common aesthetic problem. The plasma skin regeneration can be used to treat this condition by providing the energy to create thermal effect on the skin. Most of the previous PSR studies focus on medium and high energy treatment. There was a study which was done by Bernstein<sup>17</sup> used very low energy, using 0.5 J, three times at a 3-week interval full-face treatment in 12 volunteers in cutaneous photodamaged skin, the result showed that there was minimum of 25% reduction in physician wrinkle score at



**FIGURE 4** To demonstrate mean melanin index at baseline, 3-week, 6-week, 14-week visit of nitrogen plasma group and control group. \*Analysis of covariance (ANCOVA). P-value < 0.05, determined as significant value

**TABLE 1** Adverse effects

Adverse effect	1st treatment N (%)	2nd treatment N (%)	3rd treatment N (%)	Median duration (h)
Erythema	10 (55.6)	11 (61.1)	5 (27.8)	12
Desquamation/fine scale	1 (5.6)	1 (5.6)	3 (16.7)	48
Hyperpigmentation	1 (5.6)	2 (11.1)	0 (0)	48
Pruritus	0 (0)	1 (5.6)	0 (0)	24
Drying	0 (0)	0 (0)	2 (11.1)	36

1 month with increased improvement at 3 months, improvement in textural irregularity, and 40%-80% patient rate overall improvement. This study provides supportive evidence to the efficacy of the very low energy treatment for cutaneous photodamage. Therefore, the authors decided to conduct an experimental study for the treatment of mild-to-moderate periorbital wrinkles with low-energy plasma in Thais who have higher Fitzpatrick's skin type.

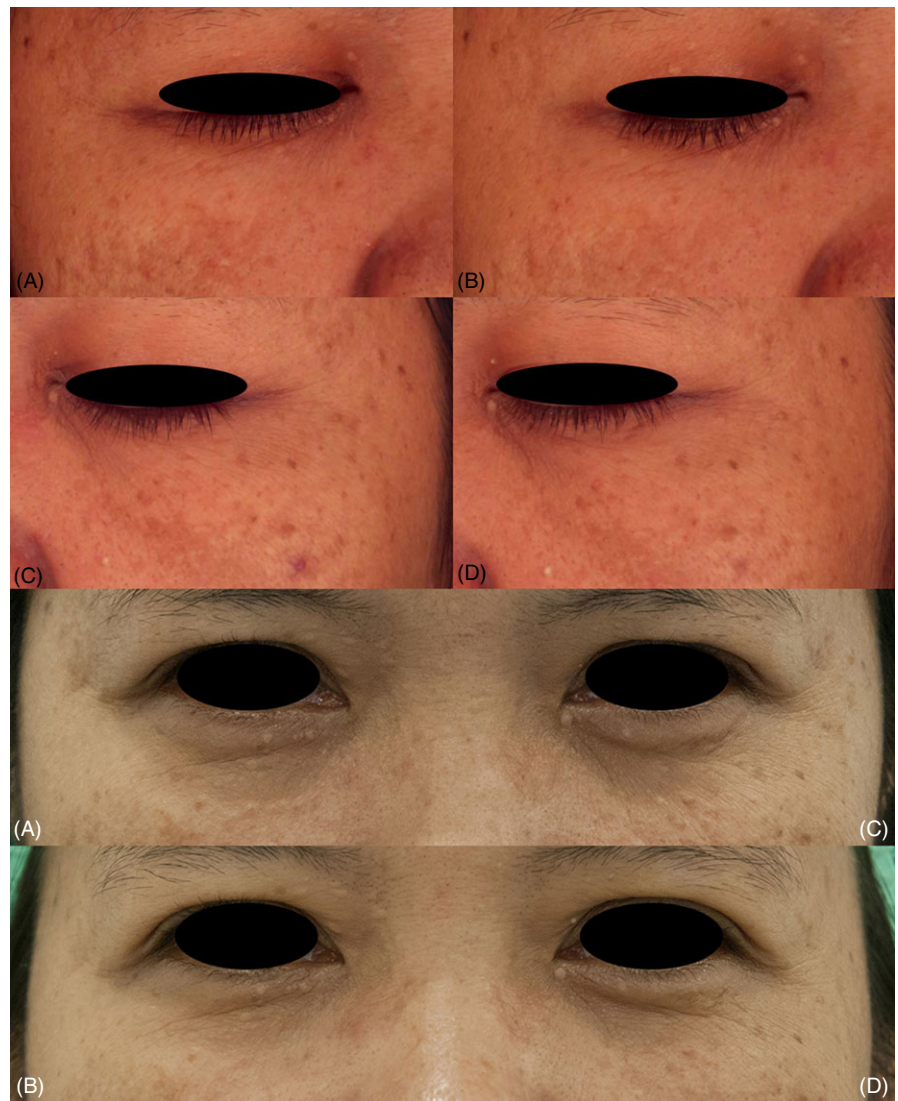
From our study, there was an improvement in the appearances of periorbital wrinkles at 3-week visit after the treatment measuring by melanin index and SEw score by Visioscan® VC 98. However, clinical improvement was seen at 14-week visit after treatment. According to the study by Foster et al,<sup>10</sup> there were immediate effects after treatment with PSR that showed the vacuolation of the basal cell layers and cleavage between the zone of thermal damage from histology, and there were the shedding of epidermal and dermal remnants at zone of thermal modification at 4 days after treatment. Because basal cell layers are the habitats of epidermal melanocytes, shedding and dying of basal cell layer may result in decreasing melanocytes and might explain the decreasing in melanin index that was found early at 3-week visit after treatment in our study. Furthermore, the study by Foster et al<sup>10</sup> also found that 10 days after the treatment, there was intense fibroplasia in the papillary and upper reticular dermis. This change in dermis might also explain the improvement of wrinkle score that could be detected early by Visioscan® VC 98 at 3-week visit after treatment despite the absence of observable clinical improvement. The clinical improvement at 14-week visit could be explained by the study of Bogle et al<sup>11</sup> which confirmed that there was a 37% reduction in facial rhytids and a decrease in solar elastosis and an increase in neocollagenesis by histology at 12-week visit after treatment with multiple low-energy treatments in plasma skin regeneration (PSR).

Our study also showed that the adverse effects of the nitrogen plasma were relatively mild and safe for general practice. These could be explained by nonchromophore properties of PSR.

Our study was the first clinical trial using multiple treatments with lower energy of PSR for mild-to-moderate periorbital wrinkles in study volunteers with higher Fitzpatrick's skin type IV. The methodology is robust as the study is randomized, double-blinded, controlled study with well-defined methodology.

Regarding the limitations, our enrolled patients were only restricted to those with mild-to-moderate periorbital wrinkles. Our





**FIGURE 5** To demonstrate forty-eight-year-old female with moderate periorbital wrinkles at baseline. At the endpoint of study, in nitrogen plasma group (A, B) and control group (C, D). Right periorbital area: baseline (A) SEw 46.31, melanin index 524.00 and 4 weeks after three nitrogen plasma treatment (B) SEw 40.17, melanin index 504.50. Left periorbital area: baseline (C) SEw 46.70, melanin index 531 and 4 weeks after three nitrogen plasma treatment (D) SEw 42.55, melanin index 528.00

results may have limitations as to making an inference to patients with severe periorbital wrinkles.

In conclusion, our study showed that nitrogen plasma is highly effective and relatively safe for the treatment of mild-to-moderate periorbital wrinkles and darkening.

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#### ETHICAL APPROVAL

This study has been approved by the Clinical Research Ethical Committee of Srinakharinwirot University on February 9, 2017, Certificate No SWUEC/E-390/2559. The study protocol followed the

guidelines of the 1964 Helsinki declaration. All volunteers informed consent form before participating in the study.

#### CONFLICT OF INTEREST

All authors had no conflict of interest in this study.

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