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Efficacy of Low-temperature Plasma for Treatment of Facial Rejuvenation in Asian Population

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Background: Plasma, the fourth state of matter, has been widely proposed in antiaging medicine. The usage of low-temperature plasma (LTP), which converts nitrogen gas into plasma, demonstrates releasing of several growth factors and promotion of tissue regeneration. The nonchromophore-dependent property and preservation of skin architecture after treatment make LTP an interesting tool for facial rejuvenation. This study aimed to investigate the efficacy of LTP for facial rejuvenation.
Methods: A prospective cohort study involving 40 women who received full face LTP treatment once a week for 5 consecutive sessions. The melanin index, erythema index, and elasticity index were measured by Mexameter and Cutometer, respectively. The Fitzpatrick wrinkle scale and quartile grading scale were assessed by two plastic surgeons.
Results: All patients were between 26 and 55 years old and had mild-to-moderate Fitzpatrick wrinkle scale scores. The Fitzpatrick wrinkle scale scores showed a mean improvement of 0.47 and 0.89 at 4 and 12 weeks posttreatment ($P < 0.001$). Statistically significant improvements in melanin index, erythema index, and elasticity index at periorbital and perioral areas were found at 4 and 12 weeks after treatment ($P < 0.001$). Most subjects had quartile grading scale improvement of 51%–75% at 4 and 12 weeks after treatment. Patients reported a greater than 75% improvement in dyspigmentation, wrinkles, and elasticity in 60%, 50%, and 57.5% of subjects, respectively.
Conclusion: LTP is another choice for facial rejuvenation, wrinkles reduction, and dyspigmentation with significantly improved results. *(Plast Reconstr Surg Glob Open 2021;9:e3812; doi: 10.1097/GOX.0000000000003812; Published online 17 September 2021.)*

INTRODUCTION

Plasma energy is considered the fourth state of matter and defined as an ionized gas. Electrons, positive and negative ions, atoms, and neutral or charged molecules are identified in plasma. It is further characterized by temperature, type of radiation, and electric fields.[1]

In medicine, plasma energy can stimulate endothelial cells to produce and secrete growth factors such as fibroblast growth factor-2, vascular endothelial growth factor, and nitric oxide, which harmonize with other cell signaling molecules to induce cell proliferation and angiogenesis.[2,3]

For facial rejuvenation, the low-temperature plasma (LTP) device converts inert nitrogen gas to plasma. Thermal activation of fibroblasts stimulates a wound healing cascade, resulting in neocollagenesis. In contrast to ablative lasers, LTP resurfacing leaves layers of epidermis intact and acts as a natural biologic coverage that promotes recovery. LTP can be safely used in all Fitzpatrick skin types with favorable safety profiles.[4–10] Since 2006, the LTP device has been approved by the US Food and Drug Administration for treatment of rhytids, dyschromia, acne scars, and photoaged skin.[4,7,11]

In Thailand, several trials with LTP were conducted by a nonthermal plasma device that can create a low-temperature plasma beam from dielectric electrodes.[12–14] LTP removes superficial layers of skin in a smooth, nonablative, and painless manner. The intermediate dose of direct LTP (2–6 J/cm^2) had induced reparable DNA damage of normal cells within 24 hours, which resulted in the release of cell growth factors, stimulation of wound healing, and promotion of tissue regeneration.[13]

The gold standard for facial rhytids is carbon dioxide (CO_2) laser resurfacing, which has been decreasing in popularity due to its adverse effects and downtime.[1–10] Although several nonablative modalities had been developed over the years, none of them are equivalent to ablative methods.

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This study aimed to investigate the efficacy of LTP as a potential alternative for facial rejuvenation to improve elasticity and reduce fine lines, wrinkles, and dyspigmentation. Furthermore, the adverse effects were also collected. The rapid return to normal activities might be an alternative for resolving the problem after an ablative method for facial rejuvenation.

MATERIAL AND METHODS

A prospective cohort study was conducted between April 2019 and December 2019 at the outpatient department, Division of Plastic Surgery, Department of Surgery, Siriraj Hospital, Mahidol University, Thailand.

After institutional review board approval, 40 women with mild-to-moderate severity of facial aging were enrolled and assessed by two independent plastic surgeons using the Fitzpatrick wrinkle scale.[15] The inclusion criteria include patients with all skin types, aged between 25 and 60 years old, and having mild-to-moderate severity of facial aging. Exclusion criteria include history of chemical peeling, use of tretinoin, laser treatment of the face, radiofrequency or intense pulsed light treatment in the last year, women who were pregnant or breastfeeding, history of hypertrophic scar or keloid formation, active facial skin infection, history of collagen vascular disease, and botulinum toxin or filler injection within 6 months.

After written consent was obtained, photographic records were taken in standard views by a single physician (WT) at the pretreatment period and at each subsequent follow-up visit. Clinical photographic comparison of skin pigmentation and wrinkle severity were evaluated by each of two independent plastic surgeons given a score using Fitzpatrick wrinkle scale and quartile grading scale to evaluate the improvement (<25%, 25%–50%, 51%–75%, and >75% improvement). Other skin parameter measurements such as melanin index, erythema index, elasticity index, and adverse outcome were determined.

Melanin index and erythema index were measured at periorbital and perioral areas on both sides of the face, using a Mexameter MX18 (Courage & Khazaka GmbH, Cologne, Germany).[16] Elasticity index was measured using Cutometer Dual MPA580 (Courage & Khazaka GmbH, Cologne, Germany). In this study, we analyzed the elasticity index with R2 and R7 parameters; both were used for assessing skin elasticity and aging when deforming the skin mechanically.[16]

The measuring points were done at four points within the periorbital area. The first point is one-third of the length of the superciliary arch on the upper eyelid, the second point is 2 cm lateral to the outer corner of the eye, the third point is 2 cm below the outer corner of the eye, and the fourth point is 2 cm below the pupil on the lower eyelid. For perioral areas, two points were measured. The first point is 1 cm lateral to oral commissure, and the second point is 3 cm slightly deviated from the oral commissure (Fig. 1).

Before each LTP session, the skin was cleansed to remove all cosmetics. The LTP device, a commercial BIOPlasma jet (PhotoBioCare, Nonthaburi, Thailand) was used at an energy setting of 4 J for 20 minutes. All participants were assigned full face treatment once a week for five consecutive sessions. The treatment interval was determined according to the time of epidermal recovery.[2,10]

After the procedure was done, the patients were advised to avoid sunlight exposure. Petrolatum-based ointment was prescribed and sunscreen (SPF 50, PA+++) was suggested for posttreatment application. The patient was free to return home after the procedure.

STATISTICAL ANALYSIS

Descriptive findings such as Fitzpatrick wrinkle scale and quartile grading scale were analyzed in mean value with SD. The differences between measurements were analyzed using a paired *t*-test. Results were presented with mean and SD unless indicated.

The significance of variations in the measurement for each time point was analyzed with the application of repeated measures ANOVA and generalized estimating equation to assess the correlation between results. Statistical analysis of the data was performed by IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y.) Results with a *P* value less than 0.05 were statistically significant.

RESULTS

The study included 40 women, aged between 26 and 55 years, with mild-to-moderate Fitzpatrick wrinkle scale. The effect of treatment was determined by a photographic

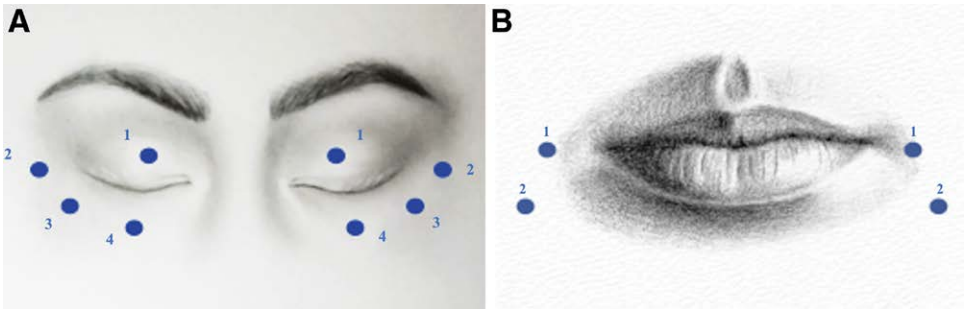

Fig. 1. Melanin index, erythema index, and elasticity index were measured at periorbital and perioral areas on both sides of the face. All of indexes were measured in the same manner. The reference points of Mexameter and Cutometer measurements at periorbital (A) and perioral (B), respectively.

comparison by one of two independent plastic surgeons. The Fitzpatrick wrinkle scale has mean improvement of 0.47 and 0.89 at 4 weeks and 12 weeks after treatment completion ($P < 0.001$) (Table 1). Quartile grading scale of 51%–75% improvement was reported in 16 and 25 patients at 4 and 12 weeks after the fifth LTP session, respectively (Table 2).

The melanin index was significantly decreased at the fourth and 12th week after treatment in the periorbital area compared with pretreatment values (217.1 ± 47.8 versus 250.1 ± 48.5) and (207.3 ± 43.2 versus 250.1 ± 48.5) ($P < 0.001$), respectively. At the perioral area, the melanin index was also significantly decreased at the fourth and 12th week after treatment compared with the value before treatment (207.8 ± 45.5 versus 262.3 ± 57.3) and (193.0 ± 42.1 versus 262.3 ± 57.3) with $P < 0.001$ (Table 3, Fig. 2).

The erythema index was statistically significantly decreased at the fourth and 12th week after treatment in the periorbital area compared with the value before treatment (283.6 ± 48.4 versus 315.9 ± 56.4) and (274.9 ± 44.6 versus 315.9 ± 56.4) ($P < 0.001$). For the perioral area, the erythema index was also significantly decreased at the fourth and 12th week after treatment compared with the value before treatment (276.5 ± 59.3 versus 332.2 ± 63.4) and (259.9 ± 57.1 versus 332.2 ± 63.4) with $P < 0.001$ (Table 3 and Fig. 3).

For the elasticity index, the R2 parameter from all reference points at the periorbital area was significantly improved at 4 and 12 weeks after treatment compared with baseline values (0.84 ± 0.06 versus 0.70 ± 0.11) and (0.86 ± 0.05 versus 0.70 ± 0.11) ($P < 0.001$). The R7 parameter from periorbital area was also improved with statistical significance at 4 and 12 weeks after treatment compared with baseline values (0.58 ± 0.11 versus 0.46 ± 0.12) and (0.61 ± 0.11 versus 0.46 ± 0.12) ($P < 0.001$) (Table 3). The perioral area had increased elasticity index in both the R2 and R7 parameters as well. The more value near 1, the more elasticity of skin was. At the fourth week, The R2 parameters were significantly improved (0.83 ± 0.06 versus 0.69 ± 0.11) and (0.84 ± 0.05 versus 0.69 ± 0.11) at the 12th week after treatment compared with the baseline values ($P < 0.001$). The R7 parameter was also improved at the fourth week (0.52 ± 0.09 versus 0.47 ± 0.10, $P < 0.014$). However, at the 12th week, the value was significantly improved (0.54 ± 0.07 versus 0.47 ± 0.10) ($P < 0.001$).

Regarding patient questionnaire after completion of treatment at 12 weeks, three patients (7.5%) reported a 25%–50% improvement in dyspigmentation (hyperpigmentation, redness), 13 patients (32.5%) showed a 51%–75% improvement, and 24 patients (60%) manifested a more than 75% improvement (Table 4, Figs. 4–7). Nine patients (22.5%) reported a 25%–50% improvement of wrinkles and fine lines, 11 patients (27.5%) reported an

Table 1. Clinical Improvement Using the Fitzpatrick Wrinkle Scale at the Fourth and 12th Week after Treatment Compared with Baseline

Week	Fitzpatrick Classification	n	Pretreatment Score	Posttreatment Score	Average Score Reduction	P
4	I	22	2.20 ± 0.59	1.89 ± 0.67	0.31	0.001
	II	18	4.86 ± 0.89	4.19 ± 0.99	0.67	0.000
	Mean score	40	3.40 ± 1.52	2.93 ± 1.42	0.47	0.000
12	I	22	2.20 ± 0.59	1.50 ± 0.67	0.7	0.000
	II	18	4.86 ± 0.89	3.75 ± 0.69	1.11	0.000
	Mean score	40	3.40 ± 1.52	2.51 ± 1.32	0.89	0.000

All results were statistically significantly improved with $P < 0.001$.

Table 2. Clinical Improvement Using Quartile Grading Scale Compared with Baseline

Improvement	Week 4	Week 12
<25%	2	1
25%–50%	8	7
51%–75%	16	25
>75%	14	7
Total patients	40	40

The majority of patients reported 51%–75% improvement after 4 and 12 weeks.

Table 3. The Melanin Index, Erythema Index, and Elasticity Index at the Fourth and 12th Week after Treatment compared with before Treatment Values in Mean ± SD

Index	Pretreatment	Week 4	P	Week 12	P
Melanin index					
Periorbital area	250.1 ± 48.5	217.1 ± 47.8	<0.001	207.3 ± 43.2	<0.001
Perioral area	262.3 ± 57.3	207.8 ± 45.5	<0.001	193.0 ± 42.1	<0.001
Erythema index					
Periorbital area	315.9 ± 56.4	283.6 ± 48.4	<0.001	274.9 ± 44.6	<0.001
Perioral area	332.2 ± 63.4	276.5 ± 59.3	<0.001	259.9 ± 57.1	<0.001
Elasticity index					
Eye R2	0.70 ± 0.11	0.84 ± 0.06	<0.001	0.86 ± 0.05	<0.001
Eye R7	0.46 ± 0.12	0.58 ± 0.11	<0.001	0.61 ± 0.11	<0.001
Mouth R2	0.69 ± 0.11	0.83 ± 0.06	<0.001	0.84 ± 0.05	<0.001
Mouth R7	0.47 ± 0.10	0.52 ± 0.09	<0.014*	0.54 ± 0.07	<0.001

*All indexes were significantly improved at $P < 0.001$ (during fourth and 12th week) except R7 parameter at the periorbital area, which later improved at the 12th week with $P < 0.001$. R2 and R7 refer to the property of elasticity or ability to deform reversibly without loss of energy of the skin. The closer the value is to 1, the more elastic the skin is.
Eye R2 refers to R2 parameter at periorbital area; Mouth R2 refers to R2 parameter at perioral area; Eye R7 refers to R7 parameter at periorbital area; Mouth R7 refers to R7 parameter at perioral area.

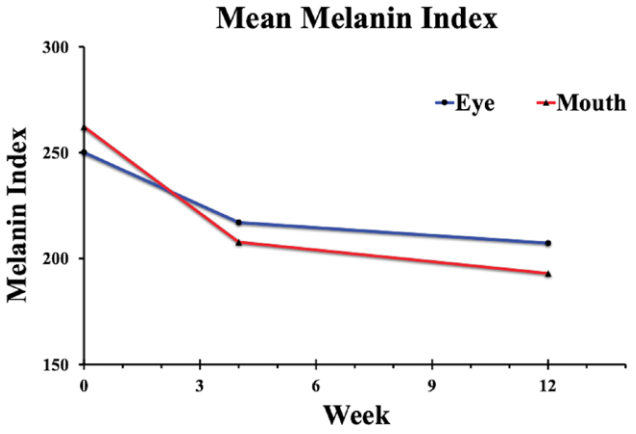

Fig. 2. The mean melanin index of reference points at periorbital and perioral areas. At the fourth and 12th weeks posttreatment, both periorbital and perioral areas had lower melanin index, which is statistically significant at $P < 0.001$, compared with pretreatment values. The index was decreasing from 4 to 12 weeks after treatment.

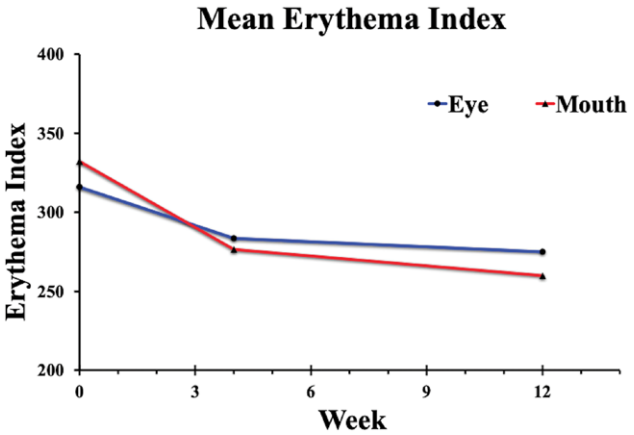

Fig. 3. The mean erythema index of reference points at periorbital and perioral areas. At 4 and 12 weeks after treatment, both periorbital and perioral areas had lower erythema index with statistical significance ($P < 0.001$) compared with pretreatment values. The indexes were still lowering from 4 to 12 weeks after treatment.

improvement in 51%–75%, and 20 patients (50%) manifested a more than 75% improvement of wrinkles and fine lines. For skin elasticity, four patients (10%) manifested improvement in 25%–50%, 13 patients (32.5%) showed improvement in 51%–75%, and 23 patients (57.5%) manifested a more than 75% improvement.

Participants had a satisfaction level at 95% for the results. About 95% of subjects would recommend the treatment to others, and 82.5% will return to receive this treatment when available. After LTP session, some patients noticed itching in 5%, transient hyperpigmentation in 7.5%, skin desquamation in 12.5%, dry skin in 55%, and redness in 30%. All side effects were mild and transiently lasting for less than 1 week. Unfortunately, one patient (2.5%) reported superficial burn at the cheek, which was completely healed in 1 week.

Table 4. Patients Questionnaire and Rating Improvement Parameters

Improvement	Dyspigmentation	Wrinkles	Elasticity
<25%	0	0	0
25%–50%	3 (7.5%)	9 (22.5%)	4 (10%)
51%–75%	13 (32.5%)	11 (27.5%)	13 (32.5%)
>75%	24 (60%)	20 (50%)	23 (57.5%)
Total patients	40	40	40

Most of subjects reported more than 75% improvement in dyspigmentation, wrinkles, and elasticity.

DISCUSSION

LTP activates endothelial production and secretion of growth factors, which result in a rejuvenating effect for the aging face. The published studies have shown that the LTP device using ablative energy settings (3–4 J) can induce skin tightening and texture improvement similar to single pass CO_2 resurfacing.[2,9,10]

Kilmer et al demonstrated an improvement in overall facial rejuvenation of 50% in 1 month.[2] Potter et al demonstrated a 24% decrease in fine lines and wrinkles at 6 months after the plasma treatment without scar, and average downtime in this study was 3 days (range 0–5).[10] Bogle et al demonstrated a 37% improvement in facial rhytids at 3 months after three sessions of low energy plasma treatment (range 1.2–1.8 J), and healing time was 5 days after

Fig. 4. Photographs of a 32-year-old patient. A, Before treatment. B, At 4 weeks after completing five sessions. C, 12 weeks after completing five sessions.

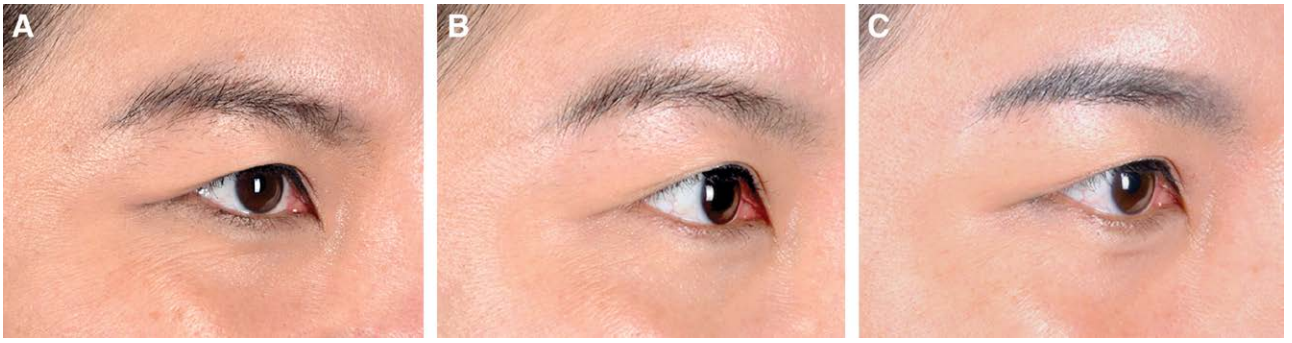

Fig. 5. Photographs of a 35-year-old patient. A, Before treatment. B, At 4 weeks after completing five sessions. C, At 12 weeks after completing five sessions.

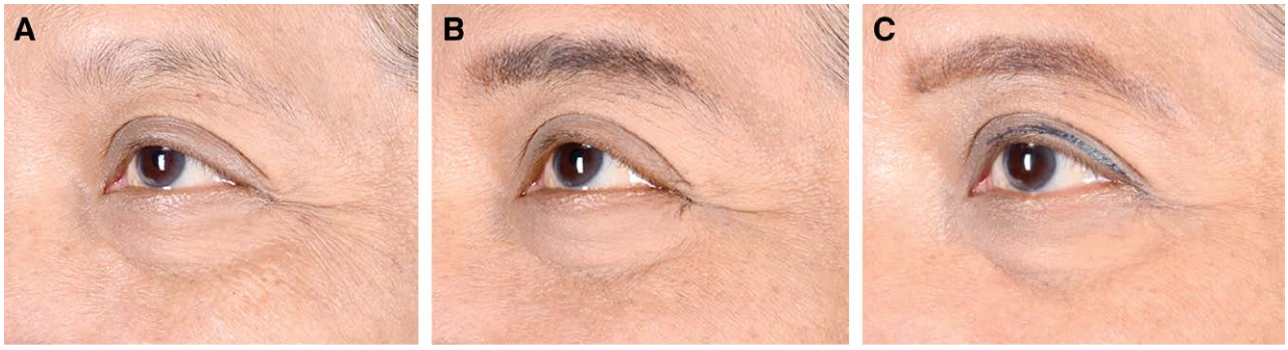

Fig. 6. Photographs of a 55-year-old patient. A, Before treatment. B, At 4 weeks after completing five sessions. C, At 12 weeks after completing five sessions.

Fig. 7. Photographs of a 55-year-old patient. A, Before treatment. B, At 4 weeks after completing five sessions. C, At 12 weeks after completing five sessions.

each session. Histologic analysis at 3 months posttreatment confirmed the neocollagenesis and dermis remodeling.[8] Techawatthanawisan et al conducted a study on the efficacy of LTP for adjunctive therapy of acne vulgaris with a significant improvement of 75% in the acne count score evaluation. Minor complaints were reported in 35% of cases, such as dry skin and debris retention.[17]

Kundilikchai et al reported the effectiveness of a LTP for reducing sebum production in oily skin. Significant sebum reduction was found in 80% of subjects.[18] Another study was conducted by Songmuang et al on the efficacy of LTP for facial rejuvenation in Thai subjects with Fitzpatrick skin type III–V. They found an insignificant difference in visual scoring scale and anti-wrinkle value. However, patient satisfaction regarding the anti-wrinkle effects on eyes and face was 80%.[19]

According to the studies which were mentioned above, both subjective and objective parameters showed a significant improvement in the Fitzpatrick wrinkle scale, melanin and erythema levels, and skin elasticity.[2,8–10,17–19] The LTP can be safely used in all Fitzpatrick skin types because it is not chromophore dependent.[9] Accordingly, this study showed that LTP improved melanin index, erythema index, and elasticity index significantly ($P < 0.001$). Furthermore, we observed the continuously positive effects of LTP at 12 weeks after treatment, which was better than the fourth week. However, further studies should be conducted to evaluate clinical differences between each session of treatment and long-term follow up to evaluate the duration of effect in facial rejuvenation of LTP.

CONCLUSIONS

The LTP is an interesting choice of treatment for facial rejuvenation. The positive effects of it have been confirmed objectively with satisfactory results and continuous improvement up to 12 weeks after treatment.

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PATIENT CONSENT

The patients provided written consent for the use of their images.

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