Combined 633-nm and 830-nm LED treatment of photoaging skin.

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Abstract

Objectives: To evaluate the clinical efficacy and ultrastructural changes in photodamaged skin after combined 633-nm and 830-nm light-emitting diode (LED) treatments.

Methods: Thirty-six subjects received 9 LED treatments over the course of 5 weeks and were subsequently evaluated for final clinical improvement 12 weeks after treatment. Five subjects were also biopsied to determine the ultrastuctural posttreatment changes in collagen fibers.

Results: A statistically significant improvement in wrinkles was seen after profilometric analysis. The majority of subjects reported improvements in softness, smoothness, and firmness at all time points. Electron microscopic analysis showed evidence of post-LED treatment of thicker collagen fibers.

Conclusions: 633-nm and 830-nm LED treatments play a role in the treatment of photodamaged skin. LED treatments can be used as either a primary or adjunctive treatment modality.

Introduction

Morphologic changes commonly associated with aging skin include development of rhytides, furrows, and telangiectasias. These features result from the composite effect of intrinsic or chronological and extrinsic, largely photodamage-related influences. (1) The clinically prominent features of aged skin are mostly attributable to photoaging rather than chronology (2) and are especially prominent in facial skin. (3-10)

Noninvasive approaches to rejuvenation are quickly becoming the preference in treatment of mild rhytides and overall skin toning. (10) Light-emitting diode (LED)-based therapy is one such treatment.

The mechanism of LED therapy involves the absorption of a specific wavelength of light by a photoacceptor molecule, which may be endogenously produced or synthesized and/or applied exogenously to the host. Irradiation of the photo-acceptor generates production of cytotoxic singlet oxygen. A cascade of cellular responses is thus initiated, resulting in modulation of cell function, cell proliferation, and possible repair of compromised cells. This process of "cell function enhancement" is called photobiomodulation. (11,12)

The selection of an appropriate wavelength is fundamental to phototherapy as cellular reactions display specificity to irradiation wavelengths. (13) Lam et al (14) demonstrated that in vitro irradiation of fibroblasts with 633-nm wavelength light increased procollagen synthesis fourfold from baseline while exhibiting no effect on the activity of the collagen-regulating proteolytic enzymes collagenase and gelatinase. Irradiation with this red light increased fibroblastic growth factor synthesis from photoactivated macrophages and accelerated mast cell degeneration. (15)

Light of 830-nm (near infrared) wavelength is absorbed in the cellular membrane rather than in cellular organelles, which remain the target when using light in the visible spectrum. This wavelength of irradiation leads to accelerated fibroblast-myofibroblast transformation and mast cell degranulation. In addition, chemotaxis and phagocytic activity of

leucocytes and macrophages are enhanced through cellular stimulation by this wavelength. (16,17)

It is likely that the synergy of 633-nm and 830-nm wavelength light will enhance fibroblast proliferation and thus increase collagen synthesis as well as stimulate inflammatory cell lines such as mast cells and macrophages. This may result in improved skin rejuvenation. The aim of this study was to assess the skin rejuvenation effects of a combination of 633-nm and 830-nm light therapy over a 12-week period in subjects presenting classic features of skin aging.

Materials and Methods

Subjects

Fifty-five subjects were recruited from the US and UK study sites. Thirty-eight subjects from this group (24 female [77%] and 7 male [23%], with an age range of 35-57 years [mean age 46.2 years]) were selected for profilometric evaluation and clinical evaluation. Five additional subjects were randomly evaluated not only for evidence of clinical improvement, but also for electron microscopic evidence of new collagen formation. Inclusion criteria were presentation of wrinkles or crow's feet in the periorbital region and photodamage of grade I-III (18) on the Glogau scale.

Subjects who had undergone laser treatment or any other ablative/nonablative cosmetic intervention within the previous 6 months, including injectables or fillers, were excluded. Subjects with any history of laser treatment or trauma to the treated sites, Fitzpatrick skin type VI individuals (19) or those on photosensitizing medications were also excluded.

The study was granted local research ethics committee approval at both the UK and US sites. All subjects gave written consent to the treatment.

Light Sources

Two separate hinged planar arrays of LEDs were used: Omnilux Revive[TM] and Omnilux Plus[TM] (Photo Therapeutics Ltd, Altringham, Manchester, UK). One delivered noncoherent but quasimonochromatic red light at a wavelength of 633 [+ or -] 3 nm and an intensity of 105 mW/[cm.sup.2], for a total dose of 126 J/[cm.sup.2] after 20 minutes of exposure. The other delivered noncoherent light at a wavelength of 830 [+ or -] 5 nm and 55 mW/[cm.sup.2] intensity, for a total dose of 66 J/[cm.sup.2] after 20 minutes of exposure.

Treatment

All subjects received a total of 9 light therapy treatments over a 5-week period. Subjects were irradiated with the 830-nm light source for 20 minutes (55 mW/[cm.sup.2], 66 J/[cm.sup.2]) on days 1, 3, 5, 15, 22, and 29. The 633-nm irradiations (105 mW/[cm.sup.2], 126 J/[cm.sup.2]), also of 20 minutes duration, were performed on days 8, 10, and 12. The light source was positioned approximately 1 cm from the subjects' faces (nose tip) for the duration of all treatments. Protective eyewear was positioned for all treatments.

Assessment

Clinical grading of wrinkles and photodamage according to the Glogau photodamage classification scale was conducted at baseline. Clinical assessment of skin smoothness using the tactile roughness grading scale (20) and Fitzpatrick scale skin type of all subjects were also recorded.

Baseline digital photography (Canon[R] 300D digicam) was performed on all subjects: 2 exposures to the bilateral periorbital regions (eyes open and closed) and 2 full-face exposures (eyes open and closed). This was repeated 6, 9, and 12 weeks after treatment. Lighting and ambient conditions for photography were standardized throughout the trial. Image analysis and photoaging assessment were conducted by an independent and blinded investigator. Bilateral cast impressions of the periorbital and temporal regions were conducted at baseline and weeks 6, 9, and 12 using Provil Novo[TM] dental impression material. Cast position was standardized at all follow-up points. Cast Analysis was conducted by profilometry at Taylor Hobson, Leicestershire, UK using a TALYSURF[R] CLI 2000 instrument with noncoherent 10-mm laser triangulation gauge. Cast analysis was performed at baseline and weeks 9 and 12. Five other treated subjects underwent 3-mm punch biopsies before and at the end of the study. All biopsies, placed in glutaraldehyde, were analyzed for ultrastructural changes in collagen fibers.

Statistical Methods

Parametric analysis of covariance (ANCOVA) was used to assess changes from baseline for each profilometry parameter, maximum depth of furrows, mean density of furrows and developed area. The model included terms for subject, time point, side (left or right periorbital region), and baseline value. The normality assumptions underlying the statistical analysis were examined using probability plots.

Results

Fifty-five subjects were screened and 43 selected for inclusion into the trial. Thirty-six subjects completed the trial. Six subjects voluntarily withdrew from the study: 4 failed to return for follow-up and 2 withdrew due to personal circumstances. One subject withdrew as a result of a mild facial herpes simplex adverse reaction. These subjects' data were excluded from analysis.

Definitions of the profilometry parameters studied are listed below Table 1. Sq measurement represents the root mean square roughness of a surface and displayed a statistically significant decrease from baseline at both 9 and 12 weeks ($P<.001$). Sa measurement showed a statistically significant decrease from baseline only at week 12 ($P<.001$). Parameters Sp ($P = .008$) and St ($P = .007$) also displayed a statistically significant decrease in post-baseline values at week 12. Measurements Sz and Sv displayed no significant changes from baseline at either time point.

In the evaluation of skin furrows, the maximum furrow depth did not alter significantly from baseline at either time point. However, the mean density of furrows, as determined by profilometry was significantly reduced at the 9-week follow-up ($P = .008$) (Table 2). Photoaging assessment scores showed significant improvement at all follow-up points (Table 3). In 51.6% of the study population, there was a 25% to 50% improvement in photoaging scores at the 12-week follow-up and a 12.9% improvement in the 50% to 75% bracket (Figures 1 to 4).

Softening of periorbital wrinkles was reported by 83.9% of subjects at 9 weeks and 80.6% at 12 weeks (Table 4). At 9 weeks, 66.8% of subjects personally reported the effect of treatment to be "excellent" or "good" in terms of periorbital wrinkle softening. At the 12-week follow-up, 58% reported this effect. In an assessment of overall tone, softness, smoothness, clarity, elasticity, and firmness of skin in the treatment area (Table 5), the majority of subjects reported improvements in softness, smoothness, and firmness at all time points. However, other assessment measures varied over time.

[FIGURE 1 OMITTED]

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During the course of follow-up, no adverse reaction scores were reported for pain, blistering, ulceration, or scarring. Mild erythema was recorded in one subject (3.2%) at day 8 and by 7 subjects (23%) at follow-up on day 15.

Electron microscopic analysis consistently showed evidence of increased thicker new collagen fibrils after treatment (Figures 5 and 6).

Discussion

Photoaged skin displays distinctive histological hallmarks. These include an overall reduction in the quantity and quality of collagen and a thickening and degradation of the dermal collagen and elastic fibers, (4-6) which produces the typical elastotic architecture of increased interfibrillary spaces seen in histological specimens of photoaged skin. The collagen fibers also become brittle and easily fragmented. (5) Dermal elastin fibers grow abundant and tortuous. (7)

It is postulated that these effects result from a combination of factors at the cellular level, which include a reduction in both the amount and biosynthetic capacity of fibroblasts, decreased proliferative capacity of skin-derived cells, and increased expression of collagen-degrading enzymes. (8)

Although highly effective, the drawbacks of ablative methodologies for skin rejuvenation, such as some chemical peels and laser resurfacing, are widely documented. The epidermal disruption associated with these treatments increases patient susceptibility to infection, and abnormal or delayed wound healing may result in scarring or altered pigmentation. (7) Patients may find the considerable downtime and persistent erythema associated with these modalities unacceptable. (9) Noninvasive approaches to rejuvenation are quickly becoming a popular approach to treating mild photodamage. (10) LED-based therapy is one such treatment.

The profilometric measurement Sq (root mean square roughness of the analysis surface) showed significant improvement of more than 13% at week 9 and 27% at week 12. The measure Sa (roughness average) displayed a significant decrease from baseline of 14% at week 12. Both Sp (maximum profile peak height) and St (maximum height of the profile) measurements displayed statistically significant decreases at week 12 of 3% and 1.2%, respectively. The cast analysis measurements generally exhibited improvements at both weeks 9 and 12, although the associated P values were not statistically significant.

Photoaging scores displayed an overall improvement in visible features of skin aging at all follow-up points. At 9 and 12 weeks follow-up, 58.1% and 51.6% of subjects, respectively, presented improvement from 25% to 50%. Improvements perceived to be 50% to 75% were seen in 16.1% and 12.9% of subjects at 9 and 12 weeks, respectively.

The subjective experience of the majority of the subjects was an overall improvement in skin softness, smoothness, and firmness in the treatment area. Electron microscopic findings were consistent with the clinical results. Subjective softening of wrinkles was consistently reported in the periorbital region (80.6% at 12 weeks). Local tolerance of the treatment was good throughout the group, with the majority of the trial subjects rating the treatment as "good to excellent."

Recent reports have shown efficacy for an LED system delivering yellow light around 595 nm. (21,22) There is no doubt that cytochrome c oxidase, the primary target in the fibroblast mitochondria for visible light, has its action spectral peak at 595 nm. However, because of the profusion of epidermal melanin and the large amount of blood present in the superficial vascular plexus, both of which are very strong photoacceptors for 595-nm light, not enough 595-nm photon density may exist at the upper- and mid-reticular dermal level to induce an optimal, clinically useful response in the fibroblasts at those levels of the dermis. Red light at 633 nm, on the other hand, penetrates living human tissue several-fold better than 595-nm light, and is also absorbed by cytochrome c oxidase. (23)

The bottom of the water absorption curve is between 820 nm and 840 nm, giving 830 nm the deepest penetration of any wavelength in living human tissue. (23) The deep penetration of both the 633-nm and 830-nm wavelengths, as well as their absorption characteristics, should ensure a clinically useful photon density in fibroblasts and other skin cells in the papillary and upper- and mid-reticular layers of the dermis.

Although the clinical results following combined 633-nm/830-nm LED irradiation can be subtle, both the profilometric results and electron microscopic findings confirm the benefits of this LED treatment. In clinical practice, LED treatments are often combined with other treatment modalities for a synergistic improvement of photodamaged skin, but our study suggests that combined 633-nm/830-nm LED treatments can be used as a primary treatment.

This study represents the first published study documenting the efficacy of combined 633-nm and 830-nm LED treatment of photodamaged skin. As is often the case for studies of new technologies, our data raise many questions. What is the respective role of 633-nm and 830-nm light? How does 633-nm and 830-nm LED treatment compare to 595-nm LED treatment? Future studies will determine if all 3 wavelengths play a synergistic role in the ideal treatment parameters. It is nonetheless clear that LED treatments do play a role in the treatment of photodamaged skin.

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Table 1. Surface Profile Measurement. Mean Profilometry Readings for Measurements Sq, Sa, Sp, St, Sv, and Sz at 9-Week and 12-Week Follow-ups.

	Sq*	Sa ([dagger])	Sp ([double dagger])
Baseline measurement	0.0655	0.0428	0.2693
Week 9 Posttreatment change from baseline (95% CI#)	0.0565 0.009 (0.013-0.005)	0.0428 0 (-0.003-0.003)	0.2563 -0.013 (-0.036-0.009)
P value	<.001	.83	.23
Week 12 Posttreatment change from baseline (95% CI#)	0.0475 0.018 (0.022-0.014)	0.037 -0.006 (-0.0009-0.003)	0.2383 -0.031 (-0.053-0.008)
P value	<.001	<.001	.008

	St ([section])	Sv ([parallel])	Sz ([paragraph])
Baseline measurement	0.60607	0.34180	0.38274
Week 9 Posttreatment change from baseline (95% CI#)	0.59007 -0.016 (-0.054-0.022)	0.3388 -0.003 (-0.033-0.027)	0.40074 0.018 (-0.004-0.04)
P value	.4	.85	.1
Week 12 Posttreatment change from baseline (95% CI#)	0.5531 -0.053 (-0.092-0.015)	0.3258 -0.016 (-0.046-0.014)	0.36674 -0.016 (-0.037-0.006)
P value	.007	.3	.14

*Sq = Root Mean Square Roughness of the Analysis Surface.

([dagger]) Sa = Roughness Average: Area Between the Roughness Profile and Its Mean Line or the Integral of the Absolute Value of the Roughness Profile Height over the Evaluation Length.
([double dagger]) Sp = Maximum Profile Peak Height.
([section]) St = Maximum Height of the Profile: The Vertical Distance From the Deepest Valley to the Highest Peak.
([parallel]) Sv = Deepest Valley of the Surface.
([paragraph]) Sz = Height of the 10 Points of the Surface.
(#) CI = Confidence Interval.

Table 2. Statistical Analysis of Furrow Measurements. Reduction from Baseline at Weeks 9 and 12.

	Surface Profile Measure	Posttreatment Reduction from Baseline (95% CI)	P Value
Week 9	Max depth (mm)	0.003 (-0.016-0.022)	.76
	Mean density (cm/[cm.sup.2])	-0.70 (-1.2- -0.19)	.008
Week 12	Max depth (mm)	-0.012 (-0.03-0.007)	.22
	Mean density (cm/[cm.sup.2])	-0.06 (-0.56-0.45)	.83

Table 3. Mean Photoaging Assessment Scores at All Follow-up Points.

Follow-up Point	0%-25% Improvement (%)	25%-50% Improvement (%)	50%-75% Improvement (%)	>75% Improvement (%)
Week 6	64.5	25.8	9.7	0
Week 9	22.6	58.1	16.1	3.2
Week 12	35.5	51.6	12.9	0

Table 4. Subject Responses in Wrinkle Softening and Overall Effect of Treatment.

Area	Time point	Softening of wrinkles (%) Yes	No	Effect of treatment (%) Excellent	Good
Periorbital region	Week 6	61.3	38.7	9.7	32.3
	Week 9	83.9	16.1	12.9	54.8
	Week 12	80.6	19.4	16.1	41.9

Area	Time point	Effect of treatment (%) Moderate	No effect	Poor
Periorbital region	Week 6	29	29	0
	Week 9	16.1	16.1	0
	Week 12	22.6	19.4	0

Table 5. Percent Subjective Reports of Improvements in Skin Measurements at All Follow-up Points.

Follow-up assessment	Tone (%)	Softness (%)	Smoothness (%)	Clarity (%)	Elasticity (%)	Firmness (%)
Week 6	48	65	68	48	35	52
Week 9	68	84	81	65	48	52
Week 12	42	65	74	45	42	48